

DESCRIPTION

CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

5 TECHNICAL FIELD

The present invention relates to new polypeptide compounds and salts thereof which are useful as a medicament.

BACKGROUND ART

10 In U.S. Pat. No. 5,376,634, 5,569,646, WO 96/11210 and WO 99/40108, there are disclosed the polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially antifungal activity).

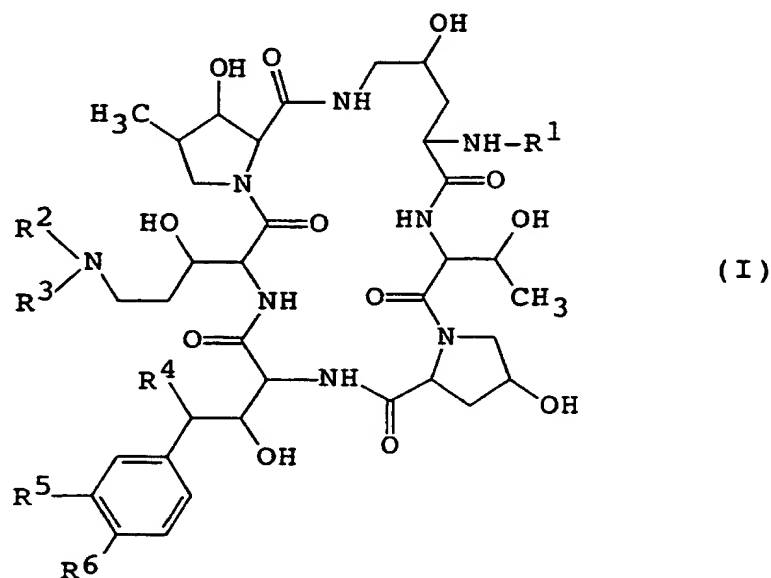
15 DISCLOSURE OF INVENTION

The present invention relates to new polypeptide compound and a salt thereof.

More particularly, it relates to new polypeptide compound and a salt thereof, which have antimicrobial
20 activities [especially, antifungal activities, in which the fungi may include Aspergillus, Cryptococcus, Candida, Mucor, Actinomyces, Histoplasma, Dermatophyte, Malassezia, Fusarium and the like.], inhibitory activity on β -1,3-glucan synthase, and further which are expected to be useful for the
25 prophylactic and/or therapeutic treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a methods for the prophylactic and/or therapeutic
30 treatment of infectious disease including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

The object polypeptide compounds of the present
35 invention are new and can be represented by the following

general formula (I):



wherein

R¹ is hydrogen or acyl group,

R² and R³ are independently hydrogen, lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s),

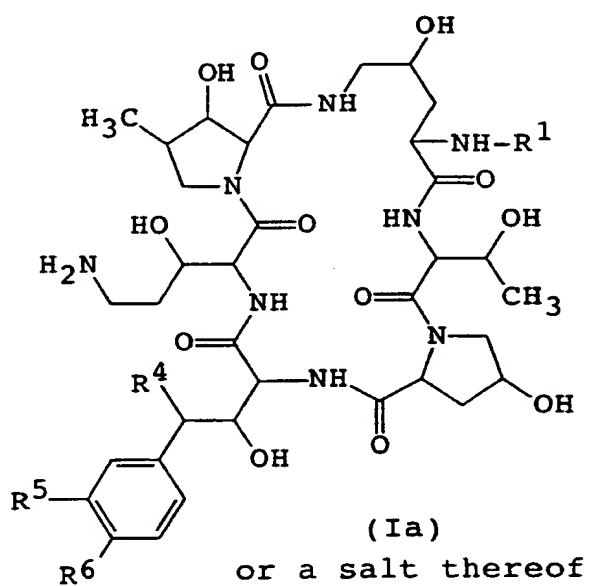
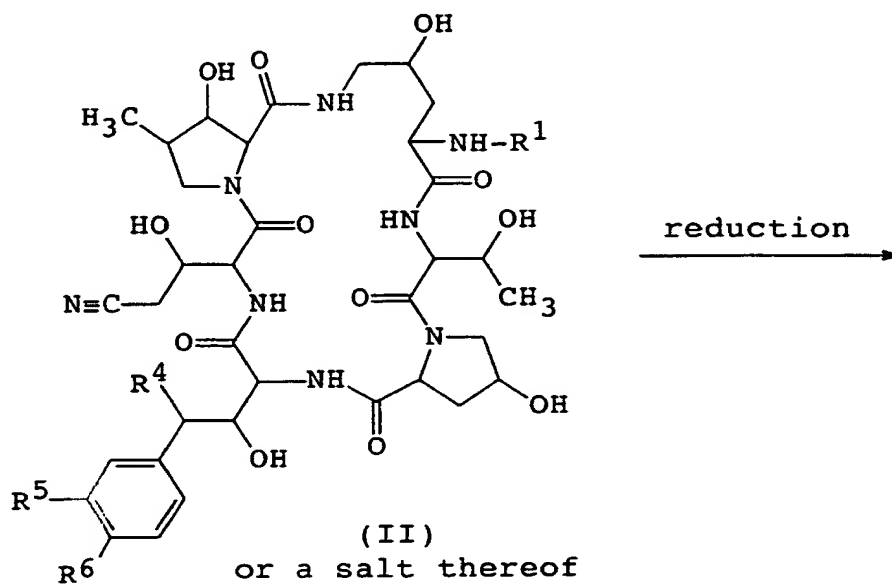
higher alkyl which may have one or more suitable substituent(s) or cyano,

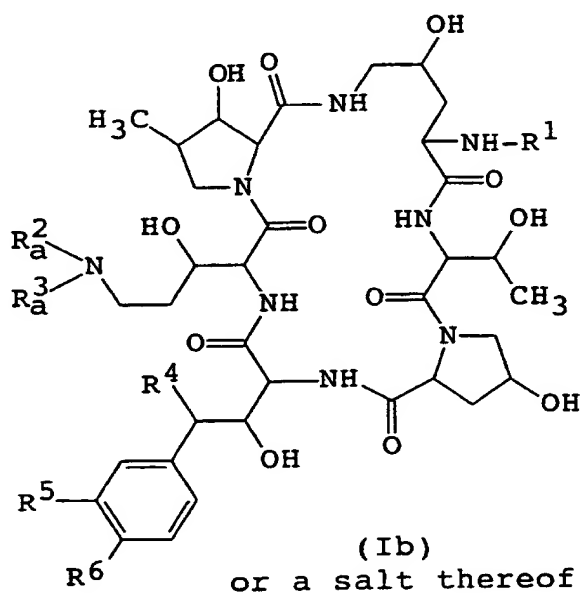
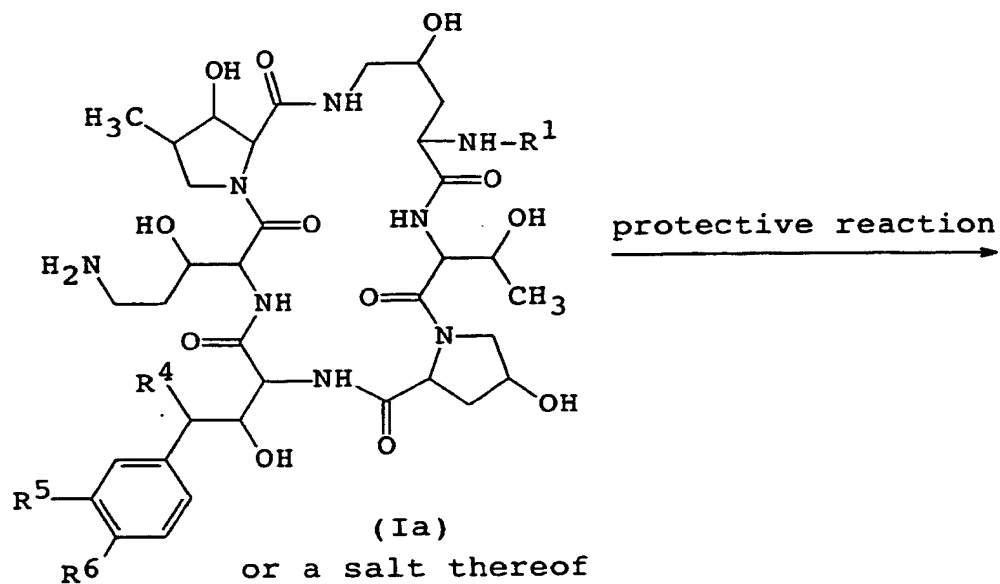
R⁴ is hydrogen or hydroxy,

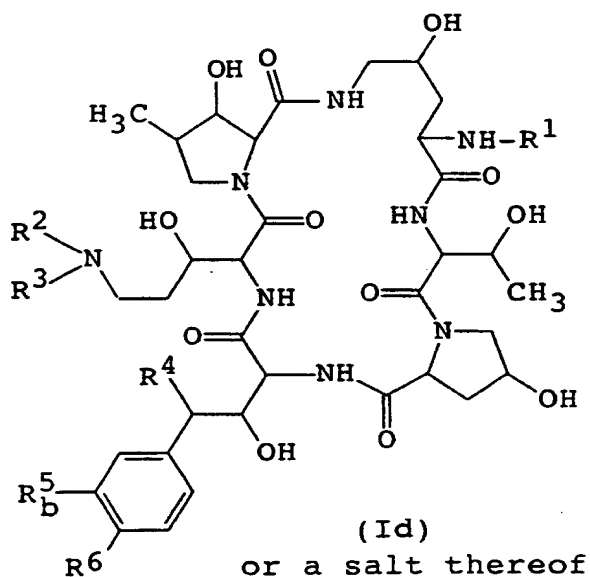
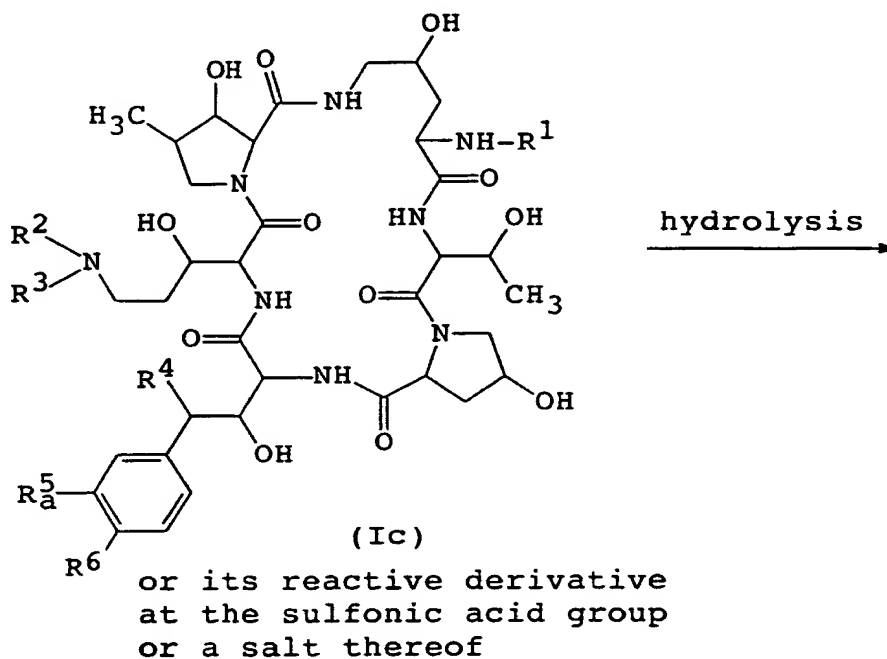
R⁵ is hydrogen, hydroxy, lower alkoxy or hydroxysulfonyloxy, and

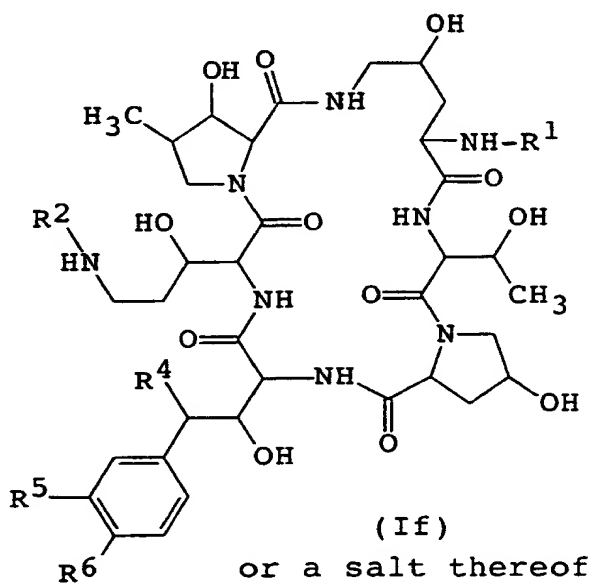
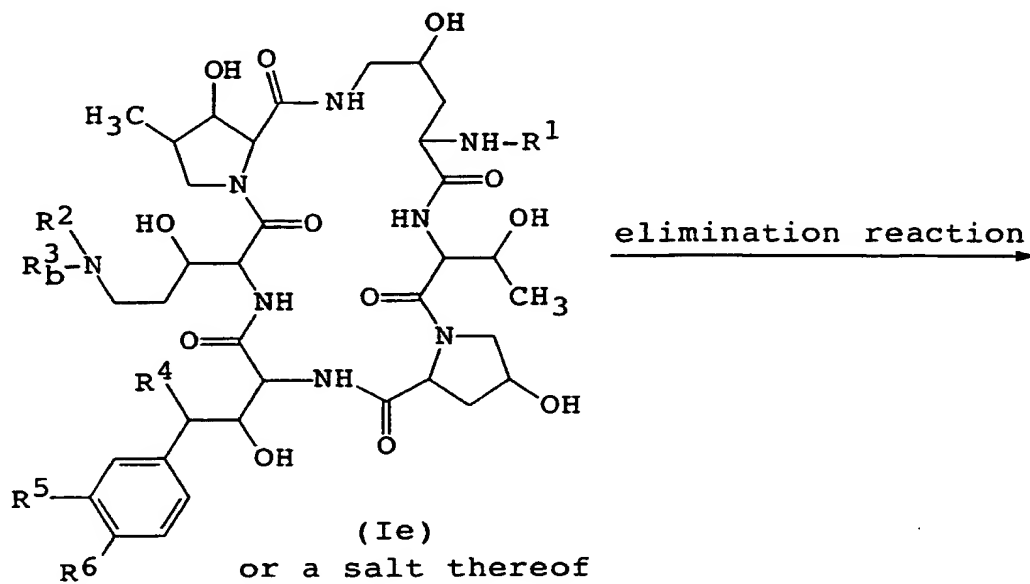
R⁶ is hydroxy or acyloxy, or a salt thereof.

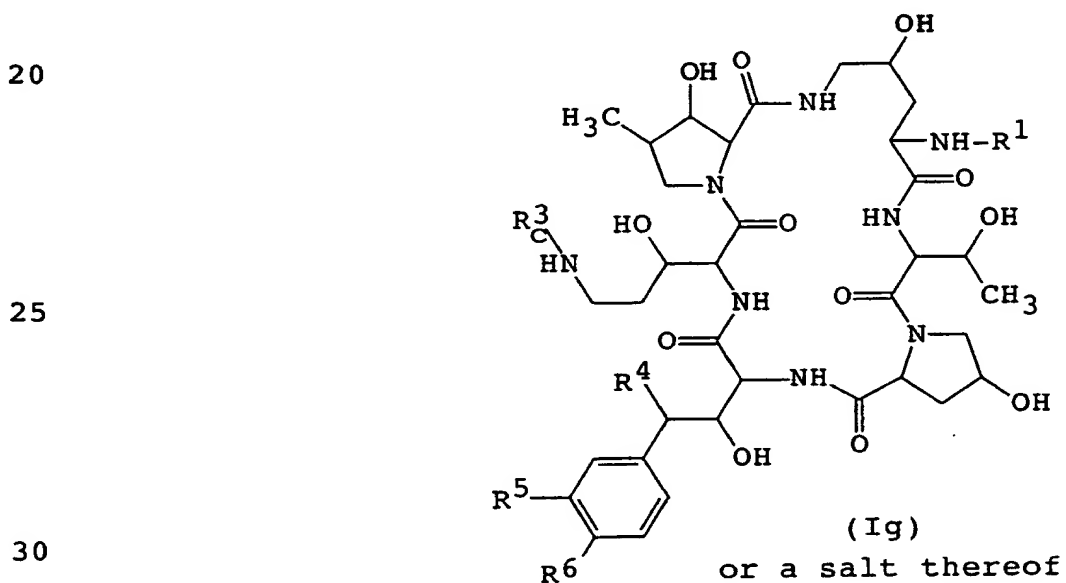
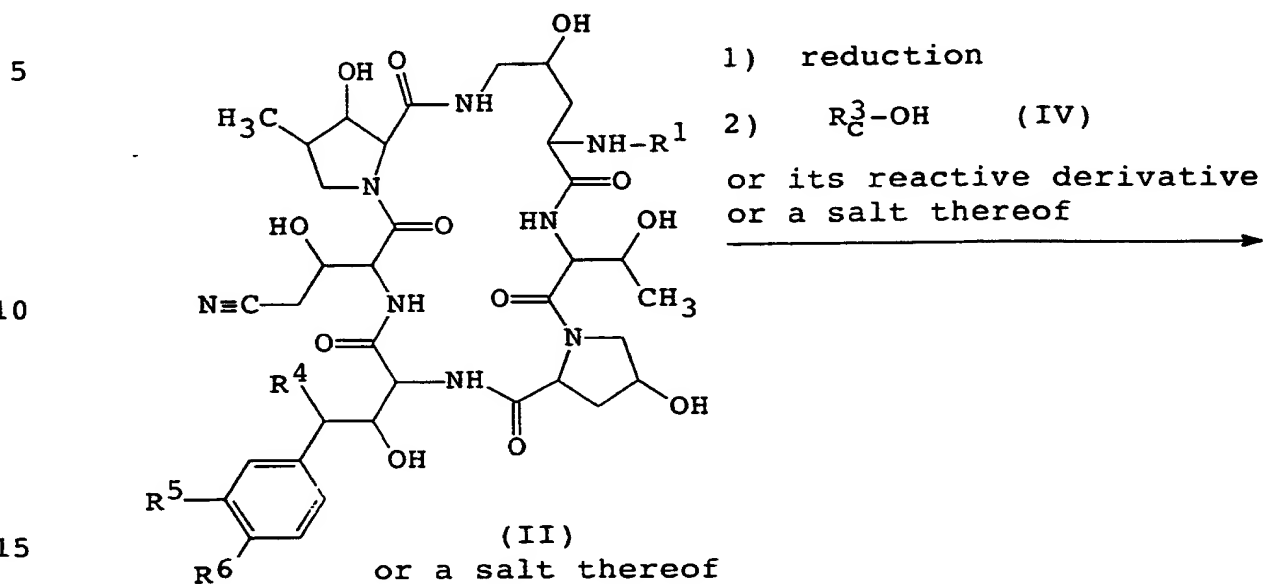
The new polypeptide compound (I) or a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

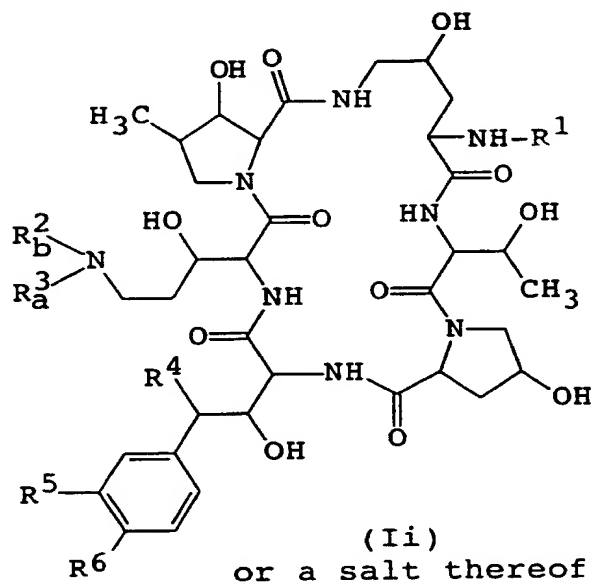
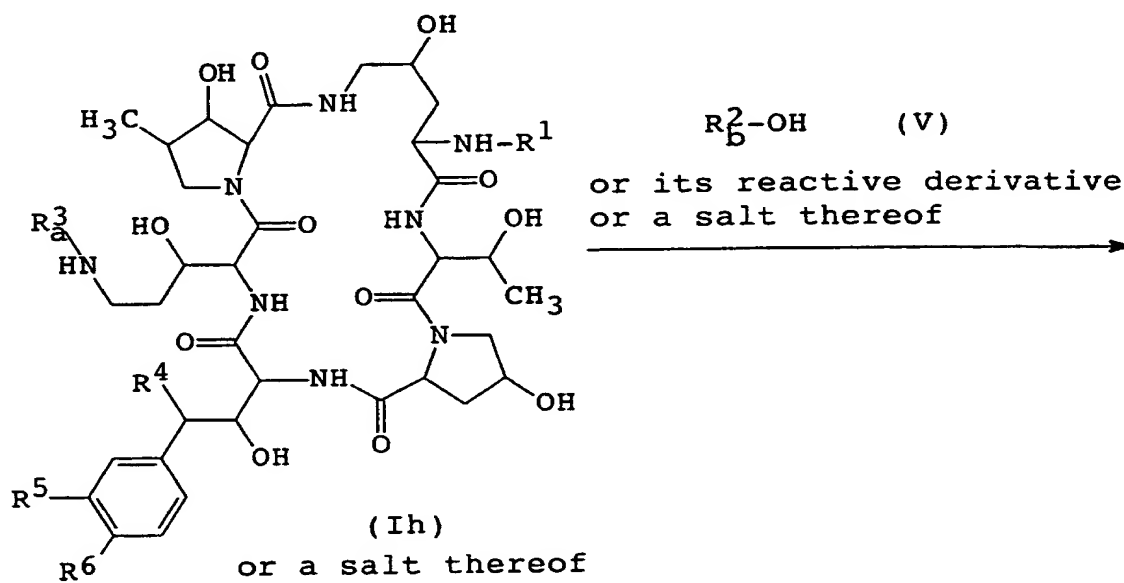
Process 1

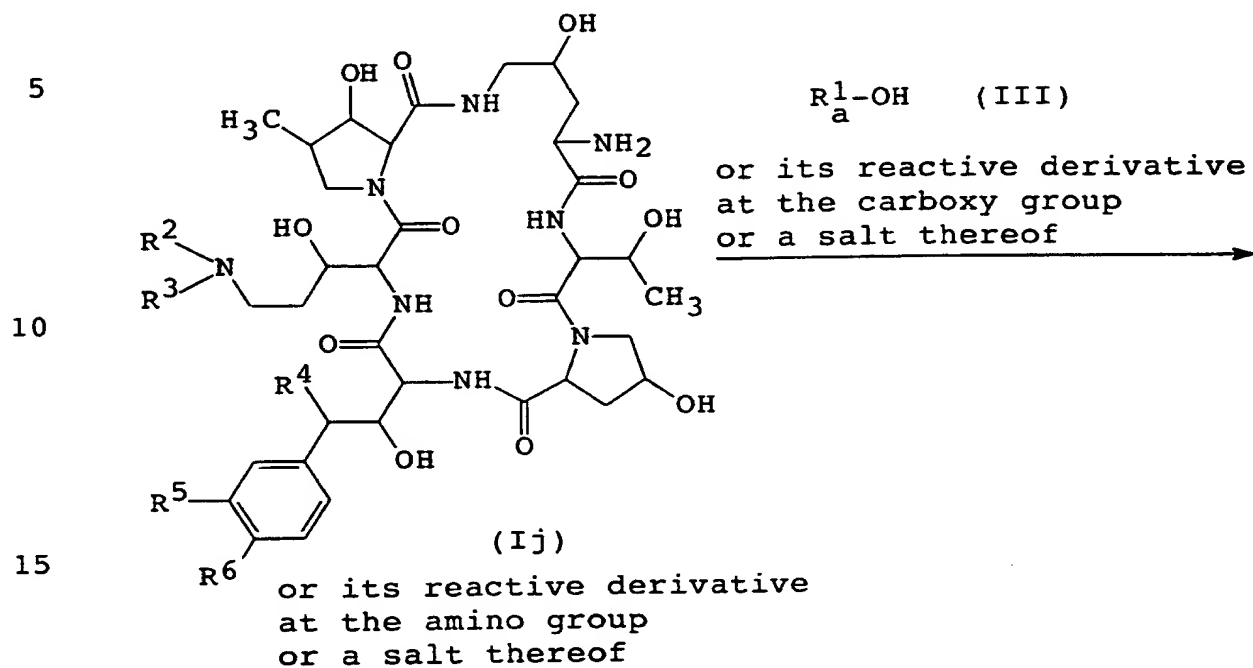
Process 2

Process 3

Process 4

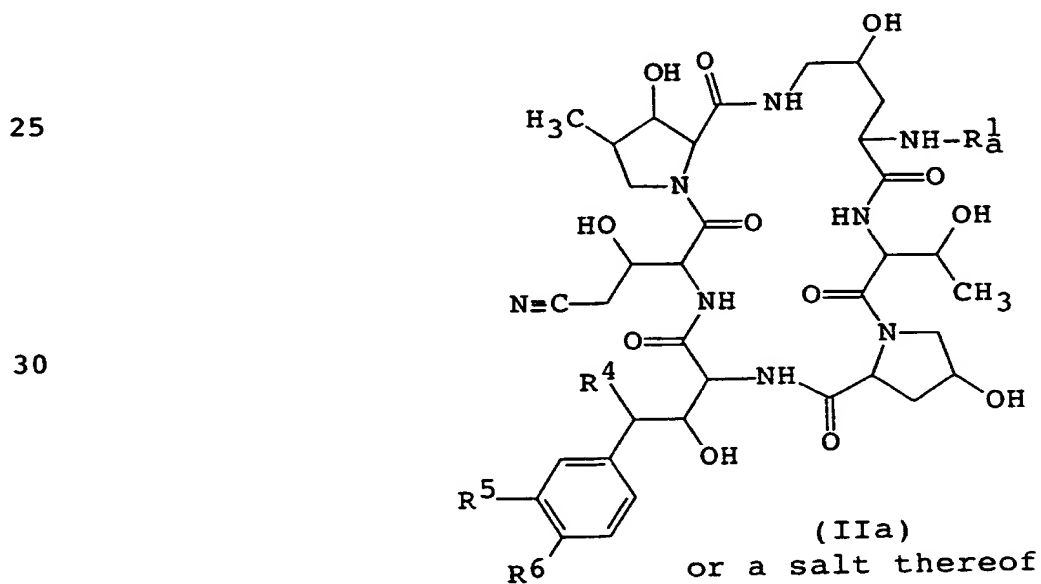
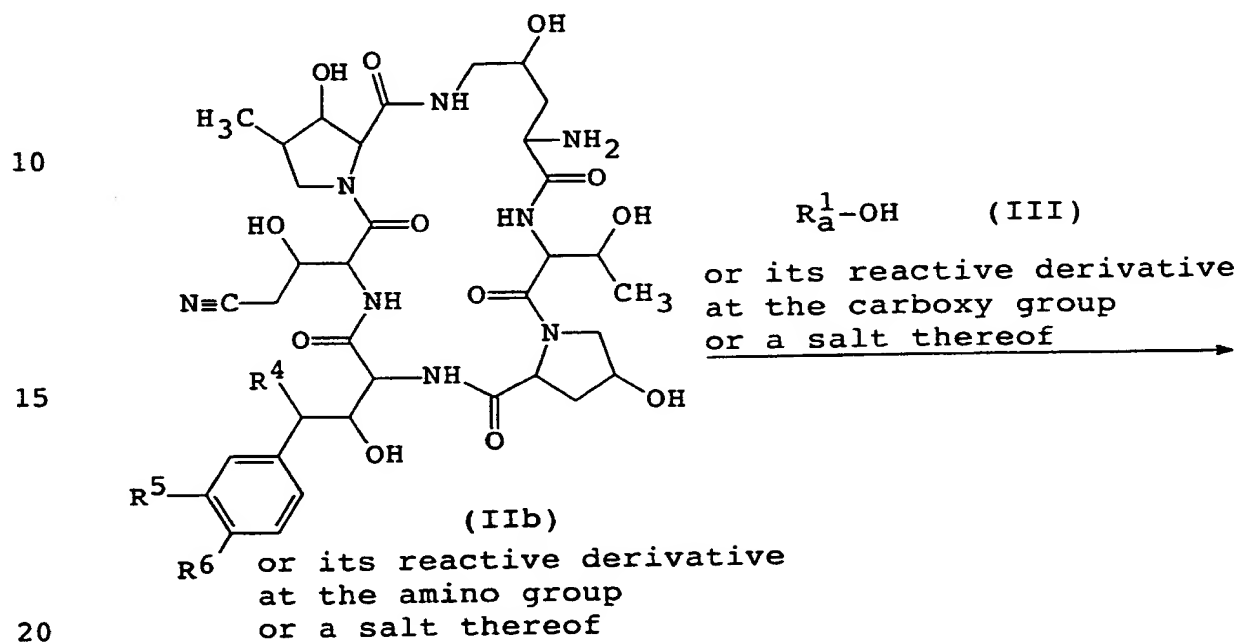
Process 5

Process 6

Process 7

The Starting compound (II) or a salt thereof can be prepared by the process as illustrated in the following reaction scheme.

5 Process A



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are defined above,

R_a^1 is acyl group,

R_a^2 is hydrogen, lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s), higher alkyl which may have one or more suitable substituent(s) or cyano,

R_b^2 is acyl group,

R_a^3 is lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s), higher alkyl which may have one or more suitable substituent(s) or cyano,

R_b^3 is amino protective group,

R_c^3 is acyl group,

R_a^5 is hydroxysulfonyloxy, and

R_b^5 is hydroxy.

Suitable salt of the new polypeptide compound (I) is a pharmaceutically acceptable and conventional non-toxic salt, and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt,

N,N'-dibenzylethylenediamine salt, 4-dimethylaminopyridine salt, etc.);

an inorganic acid addition salt (e.g., hydrochloride hydrobromide, sulfate, phosphate, etc.);

5 an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.);

10 a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

Suitable examples and illustration of the various definitions in the above and subsequent descriptions of the present specification, which the present invention intends to
15 include within the scope thereof, are explained in detail as follows:

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

20 Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 3.

Suitable example of "halogen" may be fluorine, chlorine, bromine, iodine and the like.

25 Suitable example of "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, isohexyloxy and the like.

30 Suitable example of "higher alkoxy" may include straight or branched one such as heptyloxy, octyloxy, 3,5-dimethyloctyloxy, 3,7-dimethyloctyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, and the like.

35 Suitable example of "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-

butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like.

Suitable example of "higher alkyl" may include straight or branched one such as heptyl, octyl, 3,5-dimethyloctyl, 3,7-dimethyloctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like.

Suitable example of "aryl" and "ar" moiety may include phenyl which may have lower alkyl (e.g., phenyl, mesityl, xylyl, tolyl, etc.), naphthyl, anthryl, indanyl, fluorenyl, and the like, and this "aryl" and "ar" moiety may have one or more halogen.

Suitable example of "aroyl" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl, and the like.

Suitable example of "heterocyclic group" may include unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, azetidyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyll, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, morpholino, etc.;

- 5 unsaturated condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

- 10 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

- 15 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example thiazolidinyl, thiomorpholinyl, thiomorpholino, etc.;

- 20 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, imidazothiadiazolyl, etc.;

- 25 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl etc.;

- 30 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s), for example, tetrahydrofuran, tetrahydropyran, dioxacyclopentane, dioxacyclohexane, etc.;

- 35 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s), for example benzothienyl, benzodithiynyl, etc.;

5 unsaturated condensed heterocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, benzoxathiynyl, etc.; and the like, and this "heterocyclic group" may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, oxo, cyclo(lower)alkyl, hydroxy(lower)alkyl,
10 carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl.

Suitable example of "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the
15 like, and this "cyclo(lower)alkyl" may have one or more lower alkyl.

Suitable example of "cyclo(lower)alkyloxy" may include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

20 Suitable example of "acyl group" may include aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

25 Suitable example of said "acyl group" may be illustrated as follows.

Carboxy; carbamoyl; mono or di(lower)alkylcarbamoyl (e.g., methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, etc.)

30 Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl,
35 tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl,

heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);

lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.); lower alkenyloxycarbonyl (e.g.,
5 vinyloxycarbonyl, propenyloxycarbonyl, allyloxycarbonyl, butenyloxycarbonyl, butedienyloxycarbonyl, pentenyloxycarbonyl, hexenyloxycarbonyl, etc.);

lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);

10 lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);

ar(lower)alkanoyl [e.g., phenyl(C₁-C₆)alkanoyl (e.g.,
15 phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C₁-C₆)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower)alkenoyl [e.g., phenyl(C₃-C₆)alkenoyl (e.g.,
20 phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentanoyl, phenylhexenoyl, etc.), naphthyl(C₃-C₆)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];

ar(lower)alkoxycarbonyl [e.g., phenyl(C₁-C₆)alkoxycarbonyl
25 (e.g., benzyloxycarbonyl, etc.), fluorenyl(C₁-C₆)alkoxy-carbonyl (e.g., fluorenylmethyloxycarbonyl, etc.), etc.]; aryloxycarbonyl (e.g., phenoxy-carbonyl, naphthyloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl,
30 phenoxypropionyl, etc.);

arylcarbamoyl (e.g., phenylcarbamoyl, etc.);

arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);

arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl,
etc.);

35 arylsulfonyl which may have 1 to 4 lower alkyl (e.g.,

phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl;

heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl,

5 heterocyclicpropanoyl, heterocyclicbutanoyl,

heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl,

heterocyclicbutenoyl, heterocyclicpentenoyl,

heterocyclichexenoyl, etc.);

10 heterocyclicglyoxyloyl; or the like;

in which suitable "heterocyclic" moiety in the terms

"heterocycliccarbonyl", "heterocyclic(lower)alkanoyl",

"heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl"

can be referred to aforementioned "heterocyclic" moiety, and

15 this "acyl group" may have one or more suitable

substituent(s) selected from the group consisting of lower alkyl, oxo, amino and hydroxy.

Suitable example of "acyl group" of R^1 can be referred

20 to aforementioned "acyl group", in which the preferred one may be aroyl which may have one or more suitable

substituent(s), lower alkoxycarbonyl, higher alkanoyl and heterocycliccarbonyl which may have one or more suitable substituent(s).

25

Suitable example of "suitable substituent(s)" in the term of "aroyl substituted with one or more suitable

substituent(s)" and "heterocycliccarbonyl which may have one or more suitable substituent(s)" may be heterocyclic group

30 substituted with aryl having lower alkoxy, heterocyclic group

substituted with aryl having lower alkoxy(lower)alkoxy,

heterocyclic group substituted with aryl having lower

alkoxy(higher)alkoxy, heterocyclic group substituted with

aryl having cyclo(lower)alkyloxy, heterocyclic group

35 substituted with aryl having heterocyclic group, heterocyclic

group substituted with cyclo(lower)alkyl having
cyclo(lower)alkyl, heterocyclic group substituted with aryl
having aryl substituted with lower alkoxy(lower)alkoxy,
heterocyclic group substituted with aryl having heterocyclic
5 group substituted with cyclo(lower)alkyl, heterocyclic group
substituted with aryl having aryl substituted with
heterocyclic group, heterocyclic group substituted with aryl
having aryl substituted with lower alkoxy(lower)alkyl,
heterocyclic group substituted with aryl having heterocyclic
10 group substituted with aryl(lower)alkoxy, heterocyclic group
substituted with aryl having heterocyclic group substituted
with lower alkoxy and aryl having halogen, heterocyclic group
substituted with aryl having aryl substituted with lower
alkoxy, heterocyclic group substituted with aryl having
15 cyclo(lower)alkyl, heterocyclic group substituted with aryl
having heterocyclic group substituted with aryl, heterocyclic
group substituted with aryl having heterocyclic group
substituted with aryloxy, heterocyclic group substituted with
aryl having heterocyclic group substituted with lower
20 alkoxy(lower)alkoxy, heterocyclic group substituted with aryl
having heterocyclic group substituted with lower
alkoxy(lower)alkylthio, heterocyclic group substituted with
aryl having heterocyclic higher alkoxy, heterocyclic group
substituted with aryl having heterocyclic group substituted
25 with cyclo(lower)alkyloxy, heterocyclic group substituted
with aryl having heterocyclic group substituted with aryl
having lower alkoxy(lower)alkoxy, heterocyclic group
substituted with aryl having aryloxy(lower)alkoxy,
heterocyclic group substituted with aryl having heterocyclic
30 group substituted with lower alkylthio, heterocyclic group
substituted with aryl having heterocyclic group substituted
with lower alkoxy and aryl, aryl substituted with
heterocyclic group having aryl substituted with heterocyclic
group, aryl substituted with lower alkoxy having
35 cyclo(lower)alkyl and amino, aryl substituted with

heterocyclic group having cyclo(lower)alkyl, aryl substituted with lower alkoxy having cyclo(lower)alkyl and protected amino, aryl substituted with heterocyclic group having lower alkyl, aryl substituted with aryl having lower alkoxy,

5 heterocyclic group substituted with cyclo(lower)alkyl having lower alkyl, heterocyclic group substituted with cyclo(lower)alkyl having lower alkoxy and cyclo(lower)alkyl, heterocyclic group substituted with cyclo(lower)alkyl having cyclo(lower)alkyl substituted with lower alkoxy, heterocyclic

10 group substituted with aryl having lower alkoxy(lower)alkylsulfonyl, heterocyclic group substituted with aryl having lower alkoxy(higher)alkylsulfonyl, higher alkoxy, aryl substituted with lower alkoxy(higher)alkoxy, heterocyclic group substituted with aryl having higher

15 alkoxy, heterocyclic group substituted with higher alkyl, in which the preferred one may be unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₄-C₆)-alkoxy, unsaturated 3 to 8-membered heteromonocyclic group

20 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, saturated 3

25 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)-alkoxy(C₇-C₁₄)alkoxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C₄-C₆)alkoxy,

30 unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), saturated 3 to 8-membered heteromonocyclic group

35 containing 1 to 4 nitrogen atom(s) substituted with cyclo-

- (C₄-C₆)alkyl having cyclo(C₄-C₆)alkyl, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkoxy,
- 5 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl, unsaturated condensed heterocyclic group
- 10 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having cyclo(C₄-C₆)alkyl,
- unsaturated 3 to 8-membered heteromonocyclic group
- 15 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₄-C₆)alkoxy,
- unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C₄-C₆)alkyl,
- 20 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy,
- unsaturated 3 to 8-membered heteromonocyclic group
- 25 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkyl,
- unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s)
- 30 substituted with phenyl having phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(C₁-C₄)alkyl.
- unsaturated 3 to 8-membered heteromonocyclic group
- 35 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s)

substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl having (C₁-C₄)alkyl,

5 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl.

10 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenoxy.

15 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl(C₁-C₄)alkoxy,

20 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy and chlorophenyl,

25 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,

30 unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₇-C₁₄)alkoxy,

 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₄-C₆)alkoxy,

35 unsaturated 3 to 8-membered heteromonocyclic group

- containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s)
substituted with phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy,
unsaturated 3 to 8-membered heteromonocyclic group
containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s)
5 substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy,
unsaturated 3 to 8-membered heteromonocyclic group
containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s)
substituted with phenyl having (C₇-C₁₄)alkoxy substituted
with saturated 3 to 8-membered heteromonocyclic group
10 containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s)
having di(C₁-C₄)alkyl,
unsaturated 3 to 8-membered heteromonocyclic group
containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s)
substituted with phenyl having saturated 3 to 8-membered
15 heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1
to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,
unsaturated 3 to 8-membered heteromonocyclic group
containing 1 or 2 oxygen atom(s) and 1 to 4 nitrogen atom(s)
substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)-
20 alkylsulfonyl,
saturated 3 to 8-membered heteromonocyclic group
containing 1 to 4 nitrogen atom(s) substituted with phenyl
having (C₁-C₄)alkoxy(C₄-C₆)alkoxy,
saturated 3 to 8-membered heteromonocyclic group
25 containing 1 to 4 nitrogen atom(s) substituted with phenyl
having (C₁-C₄)alkoxy substituted with phenoxy,
saturated 3 to 8-membered heteromonocyclic group
containing 1 to 4 nitrogen atom(s) substituted with phenyl
having cyclo(C₄-C₆)alkyl,
30 saturated 3 to 8-membered heteromonocyclic group
containing 1 to 4 nitrogen atom(s) substituted with phenyl
having phenyl substituted with (C₁-C₄)alkoxy(C₄-C₆)alkoxy,
saturated 3 to 8-membered heteromonocyclic group
containing 1 to 4 nitrogen atom(s) substituted with phenyl
35 having phenyl substituted with saturated 3 to 8-membered

heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,

5 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyloxy,

10 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl,

15 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy,

20 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkylthio.

25 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy(C₄-C₆)alkylthio,

30 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyl,

35 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with saturated

3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl

5 having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy and phenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
10 having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy and chlorophenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
15 having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 4 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-
20 (C₄-C₆)alkyl having (C₄-C₆)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyl having cyclo(C₄-C₆)alkyl and (C₁-C₄)alkoxy,

saturated 3 to 8-membered heteromonocyclic group
25 containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyl having cyclo(C₄-C₆)alkyl substituted with (C₁-C₄)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with
30 phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy-
35 (C₁-C₆)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)-alkoxy(C₄-C₆)alkylthio,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,

phenyl substituted with (C₁-C₄)alkoxy having cyclo-(C₄-C₆)alkyl and protected amino,

phenyl substituted with (C₁-C₄)alkoxy having cyclo-(C₄-C₆)alkyl and amino,

phenyl substituted with phenyl having (C₄-C₆)alkoxy, phenyl substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) having (C₄-C₆)alkyl,

phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl,

phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(C₁-C₄)alkyl,

phenyl substituted with condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having (C₄-C₆)alkyl,

(C₇-C₁₄)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₇-C₁₄)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl

having (C₄-C₆)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group
containing 1 to 4 nitrogen atom(s) substituted with phenyl
having saturated 3 to 8-membered heteromonocyclic group

5 containing 1 to 4 nitrogen atom(s),

xylyl substituted with (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy,
and the most preferred one may be imidazothiadiazolyl
substituted with phenyl having pentyloxy, thiadiazolyl
substituted with phenyl having methoxyhexyloxy, thiadiazolyl
10 substituted with phenyl having methoxyoctyloxy, thiadiazolyl
substituted with phenyl having methoxyheptyloxy,
imidazothiadiazolyl substituted with phenyl having
cyclohexyloxy, imidazothiadiazolyl substituted with phenyl
having dimethylmorpholino, piperazinyl substituted with
15 phenyl having methoxyheptyloxy, piperazinyl substituted with
phenyl having methoxyoctyloxy, piperazinyl substituted with
cyclohexyl having cyclohexyl, thiadiazolyl substituted with
phenyl having phenyl substituted with methoxyethoxy,
thiadiazolyl substituted with phenyl having phenyl
20 substituted with methoxybutoxy, thiadiazolyl substituted with
phenyl having phenyl substituted with ethoxypropoxy,
imidazothiadiazolyl substituted with phenyl having
piperazinyl substituted with cyclohexyl, imidazothiadiazolyl
substituted with phenyl having piperazinyl substituted with
25 cyclohexyl,

thiazolyl substituted with phenyl having pentyloxy,
thiadiazolyl substituted with phenyl having
methoxyheptyloxy,

thiadiazolyl substituted with phenyl having cyclohexyl,
30 thiadiazolyl substituted with phenyl having
cyclohexyloxy,

thiadiazolyl substituted with phenyl having phenyl
substituted with propoxy,

thiadiazolyl substituted with phenyl having phenyl
35 substituted with ethoxymethyl,

thiadiazolyl substituted with phenyl having phenyl
substituted with methoxypropoxy,

thiadiazolyl substituted with phenyl having piperazinyl
substituted with cyclohexyl,

5 thiadiazolyl substituted with phenyl having phenyl
substituted with dimethylmorpholino,

thiadiazolyl substituted with phenyl having piperazinyl
substituted with methylcyclohexyl,

10 thiadiazolyl substituted with phenyl having piperidyl,
thiadiazolyl substituted with phenyl having piperidyl
substituted with phenyl,

thiadiazolyl substituted with phenyl having piperidyl
substituted with phenoxy,

15 thiadiazolyl substituted with phenyl having piperidyl
substituted with benzyloxy,

thiadiazolyl substituted with phenyl having piperidyl
substituted with methoxy and chlorophenyl,

thiadiazolyl substituted with phenyl having
dimethylmorpholino,

20 pyrimidinyl substituted with phenyl having octyloxy,
isoxazolyl substituted with phenyl having pentyloxy,
isoxazolyl substituted with phenyl having
methoxyhexyloxy,

25 isosxazolyl substituted with phenyl having
methoxyheptyloxy,

isoxazolyl substituted with phenyl having heptyloxy
substituted with dimethylmorpholino,

isoxazolyl substituted with phenyl having octyloxy
substituted with dimethylmorpholino,

30 isoxazolyl substituted with phenyl having
dimethylmorpholino,

oxadiazolyl substituted with phenyl having pentyloxy,
oxadiazolyl substituted with phenyl having
methoxyheptyloxy,

35 oxadiazolyl substituted with phenyl having

methoxynonyloxy,

oxadiazolyl substituted with phenyl having
methoxyheptylsulfonyl,

oxadiazolyl substituted with phenyl having
5 methoxynonylsulfonyl,

piperazinyl substituted with phenyl having
methoxyhexyloxy,

piperazinyl substituted with phenyl having
methoxyheptyloxy,

10 piperazinyl substituted with phenyl having
phenoxypropoxy,

piperazinyl substituted with phenyl having cyclohexyl,

piperazinyl substituted with phenyl having phenyl
substituted with methoxypentyloxyphenyl,

15 piperazinyl substituted with phenyl having phenyl
substituted with dimethylmorpholino,

piperazinyl substituted with phenyl having piperidyl
substituted with cyclohexyloxy,

piperazinyl substituted with phenyl having piperidyl
20 substituted with phenyl,

piperazinyl substituted with phenyl having piperidyl
substituted with methoxybutoxyphenyl,

piperazinyl substituted with phenyl having piperidyl
substituted with propylthio,

25 piperazinyl substituted with phenyl having piperidyl
substituted with methoxyhexylthio,

piperazinyl substituted with phenyl having piperidyl
substituted with cyclobutanespiro,

piperazinyl substituted with phenyl having piperidyl
30 substituted with dioxacyclobutanespiro,

piperazinyl substituted with phenyl having piperidyl
substituted with methoxy and phenyl,

piperazinyl substituted with phenyl having piperidyl
substituted with methoxy and chlorophenyl,

35 piperazinyl substituted with phenyl having

dimethylmorpholino,

piperazinyl substituted with cyclohexyl having tert-butyl,

5 piperazinyl substituted with cyclohexyl having cyclohexyl and methoxy,

piperazinyl substituted with cyclohexyl having cyclohexyl substituted with propoxy,

imidazothiadiazolyl substituted with phenyl having methoxybutoxy,

10 imidazolthiadiazolyl substituted with phenyl having cyclohexyloxy,

imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

15 imidazolthiadiazolyl substituted with phenyl having piperidyl substituted with methoxypropoxy,

imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxybutoxy,

imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxypentyloxy,

20 imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxyhexyloxy,

imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxyhexylthio,

25 imidazothiadiazolyl substituted with phenyl having dimethylmorpholino,

phenyl substituted with propoxy having cyclohexyl and tert-butoxycarbonylamino,

phenyl substituted with propoxy having cyclohexyl and amino,

30 phenyl substituted with phenyl having pentyloxy,
phenyl substituted with thiazolyl having pentyl,
phenyl substituted with piperazinyl having cyclohexyl,
phenyl substituted with piperazinyl having phenyl
substituted with dimethylmorpholino,

35 phenyl substituted with bezoxazolyl having pentyl,

octyloxy,
pyrazolyl substituted with decyl,
pyrazolyl substituted with phenyl having hexyloxy,
pyrazolyl substituted with phenyl having piperidyl,
5 xylyl substituted with methoxyheptyloxy.

The more suitable example of "acyl group" may be benzoyl which has imidazolthiadiazolyl substituted with phenyl having pentyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyhexyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyoctyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyheptyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having cyclohexyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having dimethylmorpholino, benzoyl which has piperazinyl substituted with phenyl having methoxyheptyloxy, benzoyl which has piperazinyl substituted with phenyl having methoxyoctyloxy, benzoyl which has piperazinyl substituted with cyclohexyl having cyclohexyl, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with methoxyethoxy, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with methoxybutoxy, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with ethoxypropoxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl, benzoyl which has imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

benzoyl which has thiazolyl substituted with phenyl having pentyloxy,

benzoyl which has thiadiazolyl substituted with phenyl having methoxyheptyloxy,

benzoyl which has thiadiazolyl substituted with phenyl having cyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl

having cyclohexyloxy,

benzoyl which has thiadiazolyl substituted with phenyl
having phenyl substituted with propoxy,

benzoyl which has thiadiazolyl substituted with phenyl
5 having phenyl substituted with ethoxymethyl,

benzoyl which has thiadiazolyl substituted with phenyl
having phenyl substituted with methoxypropoxy,

benzoyl which has thiadiazolyl substituted with phenyl
having phenyl substituted with dimethylmorpholino,

10 benzoyl which has thiadiazolyl substituted with phenyl
having piperazinyl substituted with cyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl
having piperazinyl substituted with methylcyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl
15 having piperidyl,

benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with phenyl,

benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with phenoxy,

20 benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with benzyloxy,

benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with methoxy and chlorophenyl,

benzoyl which has thiadiazolyl substituted with phenyl
25 having dimethylmorpholino,

benzoyl which has pyrimidinyl substituted with phenyl
having octyloxy,

benzoyl which has isoxazolyl substituted with phenyl
having pentyloxy,

30 benzoyl which has isoxazolyl substituted with pentyl
having methoxyhexyloxy,

benzoyl which has isoxazolyl substituted with phenyl
having methoxyheptyloxy,

benzoyl which has isoxazolyl substituted with phenyl
35 having heptyloxy substituted with dimethylmorpholino,

benzoyl which has isoxazolyl substituted with phenyl
having octyloxy substituted with dimethylmorpholino,

benzoyl which has isoxazolyl substituted with phenyl
having dimethylmorpholino,

5 benzoyl which has oxadiazolyl substituted with phenyl
having pentyloxy,

benzoyl which has oxadiazolyl substituted with phenyl
having methoxyheptyloxy,

10 benzoyl which has oxadiazolyl substituted with phenyl
having methoxynonyloxy,

benzoyl which has oxadiazolyl substituted with phenyl
having methoxyheptylsulfonyl,

benzoyl which has oxadiazolyl substituted with phenyl
having methoxynonylsulfonyl,

15 benzoyl which has piperazinyl substituted with phenyl
having methoxyhexyloxy,

benzoyl which has piperazinyl substituted with phenyl
having methoxyheptyloxy,

20 benzoyl which has piperazinyl substituted with phenyl
having phenoxypropoxy,

benzoyl which has piperazinyl substituted with phenyl
having cyclohexyl,

benzoyl which has piperazinyl substituted with phenyl
having phenyl substituted with methoxypentyloxyphenyl,

25 benzoyl which has piperazinyl substituted with phenyl
having phenyl substituted with dimethylmorpholino,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with cyclohexyloxy,

30 benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with phenyl,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with methoxybutoxyphenyl,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with propylthio,

35 benzoyl which has piperazinyl substituted with phenyl

having piperidyl substituted with methoxyhexylthio,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with cyclobutanespiro,

benzoyl which has piperazinyl substituted with phenyl
5 having piperidyl substituted with dioxacyclobutanespiro,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with methoxy and phenyl,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with methoxy and chlorophenyl,

10 benzoyl which has piperazinyl substituted with phenyl
having dimethylmorpholino,

benzoyl which has piperazinyl substituted with
cyclohexyl having tert-butyl,

benzoyl which has piperazinyl substituted with
15 cyclohexyl having cyclohexyl and methoxy,

benzoyl which has piperazinyl substituted with
cyclohexyl having cyclohexyl substituted with propoxy,

benzoyl which has imidazothiadiazolyl substituted with
phenyl having methoxybutoxy,

20 benzoyl which has imidazothiadiazolyl substituted with
phenyl having cyclohexyloxy,

benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperazinyl substituted with cyclohexyl,

benzoyl which has imidazothiadiazolyl substituted with
25 phenyl having piperidyl substituted with methoxypropoxy,

benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxybutoxy,

benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxypentyloxy,

30 benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxyhexyloxy,

benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxyhexylthio,

benzoyl which has imidazothiadiazolyl substituted with
35 phenyl having dimethylmorpholino,

benzoyl which has phenyl substituted with propoxy having cyclohexyl and tert-butoxycarbonylamino,

benzoyl which has phenyl substituted with propoxy having cyclohexyl and amino,

5 benzoyl which has phenyl substituted with phenyl having pentyloxy,

benzoyl which has phenyl substituted with thiazolyl having pentyl,

10 benzoyl which has phenyl substituted with piperazinyl having cyclohexyl,

benzoyl which has phenyl substituted with piperazinyl having phenyl substituted with dimethylmorpholino,

benzoyl which has phenyl substituted with benzoxazolyl having pentyl,

15 benzoyl which has octyloxy,

thiadiazolylcarbonyl which has pyrazolyl substituted with decyl,

thiadiazolylcarbonyl which has pyrazolyl substituted with phenyl having hexyloxy,

20 thiadiazolylcarbonyl which has pyrazolyl substituted with phenyl having piperidyl,

piperazinylcarbonyl which has xylyl substituted with methoxyheptyloxy,

palmitoyl.

25

Suitable example of "lower alkyl" in the term of "lower alkyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkyl".

30 Suitable example of "suitable substituent(s)" in the term of "lower alkyl which may have one or more suitable substituent(s)" may be imino, amino, carbamoyl, lower alkoxy, heterocyclic group which may have one or more lower alkyl, carboxy, cyano(lower)alkylidene, lower alkylthio, sulfonic acid group, hydroxysulfonyloxy, and the like, in which the
35 preferred one may be imino, amino, carbamoyl, lower alkoxy,

pyrazolyl which may have lower alkyl, carboxy, hydroxy(lower)alkylamino which may have hydroxy(lower)alkyl, cyano(lower)alkylidene, lower alkylthio, sulfonic acid group or hydroxysulfonyloxy, and the more preferred one may be
5 imino, amino, carbamoyl, methoxy, pyrazolyl which may have methyl, carboxy, hydroxyethylamino which may have hydroxymethyl, cyanomethylidene, sulfonic acid group or hydroxysulfonyloxy.

Suitable example of "lower alkyl which may have one or
10 more suitable substituent(s)" may be iminomethyl, 1-iminoethyl, amidino, 1-imino-2-carbamoyl ethyl, 1-imino-3-methoxypropyl, carboxymethyl, 3-aminopropyl, 1-methylpyrazol-4-ylmethyl, methyl, pyrazolylmethyl having methyl, aminopropyl, aminobutyl, aminopentyl, carboxypentyl,
15 carboxymethyl, cyanomethylidenemethylthiomethyl, 2-cyano-1-methylthiovinyl, 2-cyano-1-aminovinyl, sulfopropyl, sulfobutyl, hydroxysulfonyloxypropyl and carboxyethyl.

Suitable example of "acyl group" of R^2 and R^3 can be
20 referred to aforementioned "acyl group", in which the preferred one may be lower alkanoyl, ar(lower)alkoxycarbonyl, lower alkenyloxycarbonyl, lower alkoxycarbonyl which may have lower alkanoyloxy, heterocyclic(lower)alkoxycarbonyl which may have oxo and lower alkyl, amino(lower)alkanoyl which may
25 have amino or hydroxy, heterocyclic(lower)alkanoyl which may have amino, sulfonic acid group, heterocyclic carbonyl, mono or di lower alkylcarbamoyl, and the most preferred one may be acetyl, sulfo, 2,5-diaminopentanoyl, fluorenylmethoxycarbonyl, allyloxycarbonyl, tert-
30 butoxycarbonyl, 1,3-dioxy-2-oxo-4-methyl-4-cyclopenten-5-ylmethoxycarbonyl, acetyloxymethoxycarbonyl, aminopropionyl, aminopentanoyl, aminohexanoyl, 5-amino-2-hydroxybutanoyl, 2,6-diaminohexanoyl, 2-amino-3-(pyrazol-4-yl)propionyl, morpholinocarbonyl, dimethylcarbamoyl, diethylcarbamoyl or
35 pyrrolidin-1-ylcarbonyl.

Suitable example of "suitable substituent(s)" in the term of "heterocyclic group which may have one or more suitable substituent(s)" of R^2 and R^3 may be lower alkyl, hydroxy(lower)alkyl, carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl, cyclo(lower)alkyl, oxo, and the like.

Suitable example of "heterocyclic group which may have one or more suitable substituent(s)" of R^2 and R^3 may be piperidyl which may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, hydroxy(lower)alkyl, carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl; 1,3-dioxacyclohexyl which may have one or more suitable substituent(s) selected from the group consisting of lower alkyl and cyclo(lower)alkyl; thiopyranyl which may have one or more oxo; in which the most preferred one may be N,N-dimethylpiperidyl, N-hydroxyethyl-N-methylpiperidyl, carboxypropanoylpiperidyl, 4-amino-4-carboxybutanoylpiperidyl, azetidiny carbonylpiperidyl, dimethyl-1,3-dioxacyclohexyl, cyclohexyl-1,3-dioxacyclohexyl, dioxopyranyl.

Suitable example of "lower alkylidene which may have one or more suitable substituent(s)" of R^2 and R^3 may be lower alkylidene which may have one or more lower alkylamino, in which the preferred one may be dimethylaminomethylidene.

Suitable example of "higher alkyl which may have one or more suitable substituent(s)" of R^2 and R^3 may be higher alkyl which may have one or more carboxy, in which the preferred one may be carboxyoctyl.

Suitable example of "acyl" moiety of "acyloxy" can be referred to aforementioned "acyl group", in which the preferred one may be lower alkenyloxycarbonyl, and the most

preferred one may be allyloxycarbonyl.

Suitable example of "acyloxy" may be lower alkenyloxycarbonyloxy, and the more preferred one may be allyloxycarbonyloxy.

5

Suitable example of "amino protective group" may be included in aforementioned "acyl group", a conventional protective group such as ar(lower)alkoxycarbonyl and lower alkoxycarbonyl, in which the preferred one may be phenyl-
10 (C₁-C₄)alkoxycarbonyl and fluorenyl(C₁-C₄)alkoxycarbonyl and (C₁-C₄)alkoxycarbonyl, and the most preferred one may be benzyloxycarbonyl, fluorenylmethoxycarbonyl and tert-butoxycarbonyl.

15

Suitable example of "protected amino" may be amino substituted with aforementioned "acyl group", a conventional protected amino such as ar(lower)alkoxycarbonylamino and lower alkoxycarbonylamino, in which the preferred one may be phenyl(C₁-C₄)alkoxycarbonylamino and fluorenyl(C₁-C₄)-
20 alkoxycarbonylamino and (C₁-C₄)alkoxycarbonylamino, and the most preferred one may be benzyloxycarbonylamino, fluorenylmethoxycarbonylamino and tert-butoxycarbonylamino.

Particularly, the preferred examples of the compound (I)
25 in the present invention are as follows:
the compound (I), wherein

R¹ is hydrogen; lower alkoxycarbonyl;

30 aroyl which has heterocyclic group substituted with aryl having a suitable substituent selected from the group consisting of lower alkoxy, lower alkoxy(lower)alkoxy, lower alkoxy(higher)alkoxy, aryl substituted with lower alkoxy(lower)alkoxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl substituted with lower alkoxy, aryl substituted
35 with lower alkoxy(lower)alkyl, aryl substituted

with heterocyclic group, heterocyclic group
substituted with cyclo(lower)alkyl, heterocyclic
group, heterocyclic group substituted with aryl,
heterocyclic group substituted with aryloxy,
5 heterocyclic group substituted with
ar(lower)alkoxy, heterocyclic group substituted
with lower alkoxy and aryl, higher alkoxy,
heterocyclic(higher)alkoxy, lower
alkoxy(higher)alkylsulfonyl, aryloxy(lower)alkoxy,
10 heterocyclic group substituted with
cyclo(lower)alkyloxy, heterocyclic group
substituted with aryl having lower
alkoxy(lower)alkoxy, heterocyclic group substituted
with lower alkylthio, heterocyclic group
15 substituted with lower alkoxy(lower)alkylthio, and
heterocyclic group substituted with lower
alkoxy(lower)alkoxy;

aroyl which has aryl substituted with a
suitable substituent selected from the group
20 consisting of lower alkoxy having cyclo(lower)alkyl
and amino, lower alkoxy having cyclo(lower)alkyl
and protected amino, aryl having lower alkoxy,
heterocyclic group having lower alkyl, heterocyclic
group having cyclo(lower)alkyl, and heterocyclic
25 group having aryl substituted with heterocyclic
group;

aroyl which has heterocyclic group substituted
with cyclo(lower)alkyl having one or more suitable
substituent(s) selected from the group consisting
30 of lower alkyl, lower alkoxy, cyclo(lower)alkyl,
and cyclo(lower)alkyl substituted with lower
alkoxy;

higher alkanoyl;
aroyl which has higher alkoxy; or
35 heterocycliccarbonyl which has a suitable

substituent(s) selected from the group consisting
of heterocyclic group substituted with higher
alkyl, heterocyclic group substituted with aryl
having lower alkoxy, heterocyclic group substituted
with aryl having heterocyclic group, and aryl
substituted with lower alkoxy(higher)alkoxy,
5 R^2 and R^3 are independently hydrogen;

lower alkyl which may have one or more
suitable substituent(s) selected from the group
consisting of amino, carboxy, sulfinic acid group,
10 sulfonic acid group, hydroxy(lower)alkylamino which
may have hydroxy(lower)alkyl, hydroxysulfonyloxy,
imino, lower alkoxy, oxo, lower alkylthio,
cyano(lower)alkylidene, and heterocyclic group
which may have one or more lower alkyl;

lower alkoxy carbonyl which may have one or
more suitable substituent(s) selected from the
group consisting of lower alkanoyloxy and
heterocyclic group;

20 lower alkenyloxycarbonyl;
ar(lower)alkoxy carbonyl;

lower alkanoyl which may have one or more
suitable substituent(s) selected from the group
consisting of amino, hydroxy and heterocyclic
group;

25 heterocyclic carbonyl;
mono or di(lower)alkyl carbamoyl;
sulfonic acid group;

heterocyclic group which may have one or more
suitable substituent(s) selected from the group
consisting of lower alkyl, hydroxy(lower)alkyl,
30 carboxy(lower)alkanoyl which may have amino,
heterocyclic carbonyl, cyclo(lower)alkyl, and oxo;

lower alkylidene which may have mono or di
35 lower alkylamino;

carboxy(higher)alkyl or
cyano;

R⁴ is hydrogen or hydroxy;

R⁵ is hydrogen, hydroxy, lower alkoxy or
hydroxysulfonyloxy; and

R⁶ is hydroxy or lower alkenyloxycarbonyloxy,
the more preferred one is the compound (I), wherein

R¹ is hydrogen; (C₁-C₄)alkoxycarbonyl;

benzoyl which has thiazolyl substituted with
phenyl having (C₄-C₆)alkoxy;

benzoyl which has thiadiazolyl substituted
with phenyl having a suitable substituent selected
from the group consisting of (C₁-C₄)alkoxy(C₄-C₆)-
alkoxy, phenyl substituted with (C₁-C₄)alkoxy-
(C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, cyclo-
(C₄-C₆)alkyl, cyclo(C₄-C₆)alkyloxy, phenyl
substituted with (C₁-C₄)alkoxy, phenyl substituted
with (C₁-C₄)alkoxy(C₁-C₄)alkyl, phenyl substituted
with di(C₁-C₄)alkylmorpholino, piperazinyl
substituted with cyclo(C₄-C₆)alkyl, piperazinyl
substituted with cyclo(C₄-C₆)alkyl having
(C₁-C₄)alkyl; piperidyl, piperidyl substituted with
phenyl, piperidyl substituted with phenoxy,
piperidyl substituted with benzyloxy, piperidyl
substituted with (C₁-C₄)alkoxy and chlorophenyl,
and phenyl having di(C₁-C₄)alkylmorpholino;

benzoyl which has pyrimidinyl substituted with
phenyl having (C₇-C₁₄)alkoxy;

benzoyl which has isoxazolyl substituted with
phenyl having a suitable substituent selected from
the group consisting of (C₄-C₆)alkoxy,
(C₁-C₄)alkoxy(C₄-C₆)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)-
alkoxy, (C₇-C₁₄)alkoxy substituted with di(C₁-C₄)-
alkylmorpholino, and di(C₁-C₄)alkylmorpholino;

benzoyl which has oxadiazolyl substituted with

phenyl having a suitable substituent selected from the group consisting of (C₄-C₆)alkoxy, (C₁-C₄)-alkoxy(C₇-C₁₄)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, and (C₁-C₄)alkoxy(C₇-C₁₄)alkylsulfonyl;

5 benzoyl which has piperazinyl substituted with phenyl having a suitable substituent selected from the group consisting of (C₁-C₄)alkoxy(C₄-C₆)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, phenoxy(C₁-C₄)alkoxy, cyclo(C₄-C₆)alkyl, phenyl substituted with (C₁-C₄)-
10 alkoxy(C₄-C₆)alkoxyphenyl, phenyl substituted with di(C₁-C₄)alkylmorpholino, piperidyl substituted with cyclo(C₄-C₆)alkyloxy, piperidyl substituted with phenyl, piperidyl substituted with (C₁-C₄)-alkoxy(C₁-C₄)alkoxyphenyl, piperidyl substituted
15 with (C₁-C₄)alkylthio, piperidyl substituted with (C₁-C₄)alkoxy(C₄-C₆)alkylthio, piperidyl substituted with cyclo(C₄-C₆)alkanespiro, piperidyl substituted with dioxacyclo(C₄-C₆)alkanespiro, piperidyl substituted with (C₁-C₄)alkoxy and
20 phenyl, piperidyl substituted with (C₁-C₄)alkoxy and chlorophenyl, and di(C₁-C₄)alkylmorpholino;

 benzoyl which has piperazinyl substituted with cyclo(C₄-C₆)alkyl having a suitable substituent selected from the group consisting of cyclo(C₄-C₆)-
25 alkyl, (C₄-C₆)alkyl, cyclo(C₄-C₆)alkyl and (C₁-C₄)-alkoxy, and cyclo(C₄-C₆)alkyl substituted with (C₁-C₄)alkoxy;

 benzoyl which has imidazolthiadiazolyl substituted with phenyl having a suitable
30 substituent selected from the group consisting of (C₄-C₆)alkoxy, (C₁-C₄)alkoxy(C₄-C₆)alkoxy, cyclo-(C₄-C₆)alkyloxy, piperazinyl substituted with cyclo(C₄-C₆)alkyl, piperidyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkoxy, piperidyl substituted
35 with (C₁-C₄)alkoxy(C₄-C₆)alkoxy, piperidyl

substituted with (C₁-C₄)alkoxy(C₄-C₆)alkylthio, and di(C₁-C₄)alkylmorpholino;

5 benzoyl which has phenyl substituted with a suitable substituent selected from the group consisting of (C₁-C₄)alkoxy having cyclo(C₄-C₆)-alkyl and (C₁-C₄)alkoxycarbonylamino, (C₁-C₄)alkoxy having cyclo(C₄-C₆)alkyl and amino, phenyl having (C₄-C₆)alkoxy, thiazolyl having (C₄-C₆)alkyl, piperazinyl having cyclo(C₄-C₆)alkyl, piperazinyl
10 having phenyl substituted with di(C₁-C₄)-alkylmorpholino, and benzoxazolyl having (C₄-C₆)-alkyl;

benzoyl which has (C₇-C₁₄)alkoxy;

15 thiadiazolylcarbonyl which has pyrazolyl substituted with a suitable substituent selected from the group consisting of (C₇-C₁₄)alkyl, phenyl having (C₄-C₆)alkoxy, and phenyl having piperidyl; piperazinylcarbonyl which has xylyl substituted with (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy; or
20 (C₇-C₁₄)alkanoyl;

R² and R³ are independently hydrogen;

(C₁-C₆)alkyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of amino, carboxy, sulfinic acid group, sulfonic acid group, hydroxy(C₁-C₄)alkylamino which may have
25 hydroxy(C₁-C₄)alkyl, hydroxysulfonyloxy, imino, (C₁-C₄)alkoxy, oxo, cyano(C₂-C₄)alkylidene, (C₁-C₄)alkylthio, and pyrazolyl which may have (C₁-C₄)alkyl;

30 (C₁-C₄)alkoxycarbonyl which may have (C₁-C₄)alkanoyloxy, dioxacyclo(C₄-C₆)alkenyl which may have oxo, and (C₁-C₄)alkyl;

fluorenyl(C₁-C₄)alkoxycarbonyl;

(C₂-C₄)alkenyloxycarbonyl;

35 (C₁-C₆)alkanoyl which may have 1 or 2 suitable

substituent(s) selected from the group consisting of amino, hydroxy and pyrazolyl;

pyrrolidinylcarbonyl;

morpholinocarbonyl;

5 mono or di(C₁-C₄)alkylcarbamoyl;

sulfonic acid group;

piperidyl which may have 1 or 2 suitable

substituent(s) selected from the group consisting

of (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl,

10 carboxy(C₁-C₄)alkanoyl which may have amino, and azetidylcarbonyl;

dioxacyclo(C₄-C₆)alkyl which may have 1 or 2

suitable substituent(s) selected from the group

consisting of (C₁-C₄)alkyl, and cyclo(C₄-C₆)alkyl;

15 thiopyranyl which may have 1 or 2 oxo;

(C₂-C₄)alkylidene which may have mono or

di(C₁-C₄)alkylamino;

carboxy(C₇-C₁₄)alkyl or

cyano,

20 R⁴ is hydrogen or hydroxy,

R⁵ is hydrogen, hydroxy, (C₁-C₄)alkoxy or

hydroxysulfonyloxy, and

R⁶ is hydroxy or (C₂-C₄)alkenyloxycarbonyloxy.

25 Process 1

The object compound (Ia) or a salt thereof can be prepared by reducing a compound (II) or a salt thereof.

Suitable salts of the compounds (Ia) and (II) may be the same as those exemplified for the compound (I).

30 The reaction can be carried out in a conventional manner namely, chemical reduction or catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium
35 acetate, etc.] and an organic or inorganic acid [e.g. formic

acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, hydride transfer reagent such as aluminum hydride compound (e.g. lithium aluminum hydride, lithium hydridotri-t-butoxyaluminate, etc.), borohydride compound (e.g. sodium borohydride, sodium cyanoborohydride, etc.) or the like etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.] or the like.

The reaction of this process is usually carried out in a solvent such as water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetic acid, diethyl ether, dioxane, tetrahydrofuran, methylene chloride, etc. or a mixture thereof.

The reaction is preferably carried out under somewhat milder conditions such as under cooling to warming.

It is included within the scope of the present invention that "hydroxy" in R^4 may be reduced to "hydrogen" during the reaction.

30

Process 2

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to protective reaction of amino.

35 This protective reaction may include acylation or

alkylation reaction of amino and the like, and can be carried out according to a conventional manner such as the one described in Examples or the similar manners thereto.

5 Process 3

The object compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or its reactive derivative at the sulfonic acid group or a salt thereof to hydrolysis reaction of the sulfonic acid group.

10 The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g., sodium potassium, etc.], an alkaline earth metal [e.g., magnesium, calcium, etc.], the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

20 Suitable acid may include an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], and an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

25 The elimination using Lewis acid such as trihaloacetic acid [e.g., trichloroacetic acid, trifluoroacetic acid, etc.], or the like preferably carried out in the presence of cation trapping agent [e.g., anisole, phenol, etc.].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

35 The reaction temperature is not critical and the

reaction is usually carried out under cooling to warming.

Process 4

The object compound (If) or a salt thereof can be
5 prepared by subjecting a compound (Ie) or a salt thereof to
elimination reaction of amino protective group.

This reaction is carried out in accordance with a
conventional method such as hydrolysis, reduction or the
like.

10 The hydrolysis is preferably carried out in the presence
of a base or an acid including Lewis acid. Suitable base may
include an inorganic base and an organic base such as an
alkali metal [e.g. sodium, potassium, etc.], an alkaline
earth metal [e.g. magnesium, calcium, etc.], the hydroxide or
15 carbonate or bicarbonate thereof, trialkylamine [e.g.
trimethylamine, triethylamine, etc.], picoline, 1,5-
diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane,
1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic
20 acid, acetic acid, propionic acid, trichloroacetic acid,
trifluoroacetic acid, etc.] and an inorganic acid [e.g.
hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen
chloride, hydrogen bromide, etc.]. The elimination using
Lewis acid such as trihaloacetic acid [e.g. trichloroacetic
25 acid, trifluoroacetic acid, etc.] or the like is preferably
carried out in the presence of cation trapping agents [e.g.
anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as
water, an alcohol [e.g. methanol, ethanol, etc.], methylene
30 chloride, tetrahydrofuran, a mixture thereof or any other
solvent which does not adversely influence the reaction. A
liquid base or acid can be also used as the solvent. The
reaction temperature is not critical and the reaction is
usually carried out under cooling to warming.

35 The reduction method applicable for the elimination

reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

10 Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, 15 palladium on carbon, colloidal palladium, palladium on barium, sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], 20 copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, 25 or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a 30 mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 5

The compound (Ig) or a salt thereof can be prepared by reducing the compound (II) or a salt thereof, and then reacting with the compound (IV) of the formula:

5



(wherein R_C^3 is acyl group)

or its reactive derivative, or a salt thereof.

10

Suitable reactive derivative of the compound (IV) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anydride; an activated amide with imidazole, 4-substitud imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2\overset{+}{N}=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine,

35

1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from
5 them according to the kind of the compound (IV) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide,
10 pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

When the compound (IV) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such
15 as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide); N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarboxi-
imide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-
20 cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorous
oxychloride (phosphoryl chloride); phosphorous trichloride; thionyl chloride; oxalyl chloride; triphenylphosphite;
25 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt;
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of
N,N-dimethylformamide with thionyl chloride, phosgene,
30 phosphorous oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine,
35 di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine,

etc.) N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

5

Process 6

The object compound (Ii) or a salt thereof can be prepared by reacting the compound (Ih) or a salt thereof with the compound (V) of the formula:

10



(wherein R_B^2 is acyl group)
or its reactive derivative, or a salt thereof.

15

This reaction can be carried out according to a conventional manner such as the one described in Process 5, Examples or the similar manner thereto.

20 Process 7

The object compound (Ik) or a salt thereof can be prepared by reacting the compound (Ij) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

25

Suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.

30

Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, 35 sulfuric acid, sulfonic acid [e.g., methanesulfonic acid,

etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.];

- 5 or aromatic carboxylic acid [e.g., benzoic acid, etc.];
a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole;
or an activated ester [e.g., cyanomethyl ester, methoxymethyl
10 ester, dimethyliminomethyl $[(CH_3)_2N^+=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachloropentyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl
15 thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These
20 reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the object compound (I).

- 25 The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent
30 which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

- In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably
35 carried out in the presence of a conventional condensing

- agent such as N,N'-dicyclohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide;
5 N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
N,N-carbonylbis-(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine, ethoxyacetylene;
1-alkoxy-2-chloroethylene; trialkyl phosphite;
10 ethyl polyphosphate; isopropyl polyphosphate;
phosphorus oxychloride (phosphoryl chloride);
phosphorus trichloride; thionyl chloride; oxalyl chloride;
lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl
chloroformate, etc.]; triphenylphosphine;
15 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-
sulfophenyl)isoxazolium hydroxide intramolecular salt;
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;
so-called Vilsmeier reagent prepared by the reaction of N,N-
dimethylformamide with thionyl chloride, phosgene,
20 trichloromethyl chloroformate, phosphorous oxychloride,
methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of
an inorganic or organic base such as an alkali metal
carbonate alkali metal bicarbonate, tri(lower)alkylamine
25 (e.g., triethylamine, diisopropylethylamine, etc.), pyridine,
di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine,
etc.), N-(lower)alkylmorpholine, N,N-
di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the
30 reaction is usually carried out under cooling to warming.

Process A

The object compound (IIa) or a salt thereof can be prepared by reacting the compound (IIb) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.

Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid, anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N^+=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachloropentyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive

derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the
5 object compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate,
10 N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a
15 free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
20 N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide;
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
N,N-carbonylbis-(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine, ethoxyacetylene;
25 1-alkoxy-2-chloroethylene; trialkyl phosphite;
ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride);
phosphorus trichloride; thionyl chloride; oxalyl chloride;
lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl
30 chloroformate, etc.]; triphenylphosphine;
2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt;
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;
so-called Vilsmeier reagent prepared by the reaction of
35 N,N-dimethylformamide with thionyl chloride, phosgene,

trichloromethyl chloroformate, phosphorous oxychloride, methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

10 The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The compounds obtained by the above Processes 1 to 7 and Process A can be isolated and purified by a conventional method such as pulverization, recrystallization, column-chromatography, high-performance liquid chromatography (HPLC), reprecipitation, desalting resin column chromatography, or the like.

15 The compounds obtained by the above Processes 1 to 7 and Process A may be obtained as its solvate, such as hydrate, and its solvate, such as hydrate is included within the scope of the present invention.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and the mixture thereof are included within the scope of the present invention.

25 The object compound (I) or a salt thereof may include solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compound (I) or a salt thereof may include both its crystal form and non-crystal form.

It should be understood that the compounds in the present invention may include the prodrug form.

35

The patent applications and publications cited herein are incorporated by reference.

Biological property of the polypeptide
compound (I) of the present invention

In order to show the usefulness of the polypeptide compound (I) of the present invention, the biological data of the representative compound is explained in the following.

Test (Antimicrobial activity):

In vitro antimicrobial activity of the object compound of Example 5 disclosed later was determined by MIC_S in mouse serum as described below.

Test Method:

The MIC_S in mouse serum were determined by the microdilution method using ICR mouse serum buffered with 20 mM HEPES buffer (pH 7.3) as a test medium. Inoculum suspension of 10⁶ cells/ml were prepared by a hemocytometric procedure and diluted to obtain an inoculum size of approximately 1.0 x 10³ cells/ml. Microplates were incubated at 37°C for 24 hours in 5% CO₂. The MIC_S were defined as the lowest concentrations at which no visible growth was observed.

Test Result:

MIC (μg/ml)

Test compound Test organism	The object compound of <u>Example 5</u>
Candida albicans FP-633	<0.3

From the test result, it is realized that the object compound (I) of the present invention has an antimicrobial activity (especially, antifungal activity).

In more details, the object compound (I) of the present invention have an antifungal activity, particularly against the following fungi.

5

Acremonium;

Absidia (e.g., *Absidia corymbifera*, etc);

Aspergillus (e.g., *Aspergillus clavatus*, *Aspergillus flavus*,

Aspergillus fumigatus, *Aspergillus nidulans*, *Aspergillus*

10

niger, *Aspergillus terreus*, *Aspergillus versicolor*, etc);

Blastomyces (e.g., *Blastomyces dermatitidis*, etc);

Candida (e.g., *Candida albicans*, *Candida glabrata*, *Candida*

guilliermondii, *Candida kefyr*, *Candida krusei*, *Candida*

parapsilosis, *Candida stellatoidea*, *Candida tropicalis*,

15

candida utilis, etc.);

Cladosporium (e.g., *Cladosporium trichloides*, etc);

Coccidioides (e.g., *Coccidioides immitis*, etc);

Cryptococcus (e.g., *Cryptococcus neoformans*, etc);

Cunninghamella (e.g., *Cunninghamella elegans*, etc);

20

Dermatophyte;

Exophiala (e.g., *Exophiala dermatitidis*, *Exophiala spinifera*, etc);

Epidermophyton (e.g., *Epidermophyton floccosum*, etc);

Fonsecaea (e.g., *Fonsecaea pedrosoi*, etc);

25

Fusarium (e.g., *Fusarium solani*, etc);

Geotrichum (e.g., *Geotrichum candidum*, etc);

Histoplasma (e.g., *Histoplasma capsulatum* var. *capsulatum*, etc).

Malassezia (e.g., *Malassezia furfur*, etc);

30

Microsporum (e.g., *Microsporum canis*, *Microsporum gypseum*, etc);

Mucor;

Paracoccidioides (e.g., *Paracoccidioides brasiliensis*, etc);

Penicillium (e.g., *Penicillium marneffe*, etc);

35

Phialophora;

- Pneumocystis* (e.g., *Pneumocystis carinii*, etc);
Pseudallescheria (e.g., *Pseudallescheria boydii*, etc);
Rhizopus (e.g., *Rhizopus microsporus* var. *rhizopodiformis*,
Rhizopus oryzae, etc);
5 *Saccharomyces* (e.g., *Saccharomyces cerevisiae*, etc);
Scopulariopsis;
Sporothrix (e.g., *Sporothrix schenckii*, etc);
Trichophyton (e.g., *Trichophyton mentagrophytes*, *Trichophyton*
rubrum, etc);
10 *Trichosporon* (e.g., *Trichosporon asahii*, *Trichosporon*
cutaneum, etc).

The above fungi are well-known to cause various
infection diseases in skin, hair, nail, oral mucosa,
15 gastrointestinal tract, bronchus, lung, endocardium, brain,
meninges, urinary organ, vaginal protion, oral cavity,
ophthalmus, systemic, kidney, bronchus, heart, external
auditory canal, bone, nasal cavity, paranasal cavity, spleen,
liver, hypodermal tissue, lymph doct, gastrointestinalne,
20 articulation, muscle, tendon, interstitial plasma cell in
lung, and so on.

Therefore, the object compound (I) of the present
invention are useful for preventing and treating various
25 infectious diseases, such as dermatophytosis (e.g.,
trichophytosis, etc), pityriasis versicolor, candidiasis,
cryptococcosis, geotrichosis, trichosporosis, aspergillosis,
penicilliosis, fusariosis, zygomycosis, sporotrichosis,
chromomycosis, coccidioidomycosis, histoplasmosis,
30 blastomycosis, paracoccidioidomycosis, pseudallescheriosis,
mycetoma, mycotic keratitis, otomycosis, pneumocystosis, and
so on.

The pharmaceutical composition of the present invention
35 can be used in the form of a pharmaceutical preparation, for

example, in solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for
5 rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

10 The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams; ointments; aerosols; powders for insufflation; in a liquid
15 form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents;
20 perfumes or buffer; or any other commonly may be used as additives.

The object compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired
25 antimicrobial effect upon the process or condition of diseases.

For applying the composition to humans, it is preferable to apply it by intravenous, intramuscular, pulmonary, oral administration, eye drop administration or insufflation.
30 While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-20 mg of the object compound (I) per kg weight of human being
35 in the case of intramuscular administration, a daily dose of

0.1-20 mg of the object compound (I) per kg weight of human being, in case of oral administration, a daily dose of 0.5-50 mg of the object compound (I) per kg weight of human being is generally given for treating or preventing infectious diseases.

Especially in case of the treatment of prevention of Pneumocystis carinii infection, the followings are to be noted.

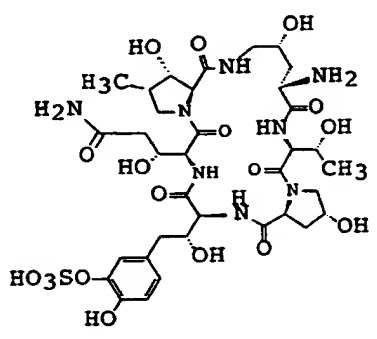
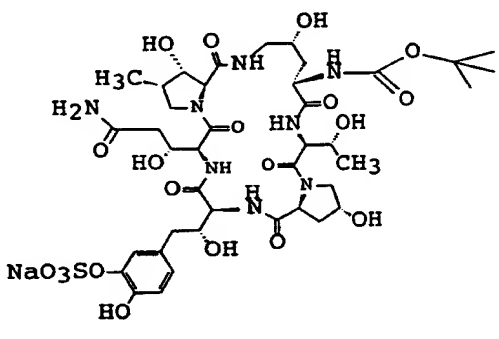
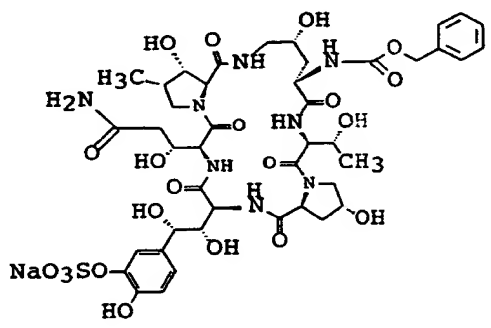
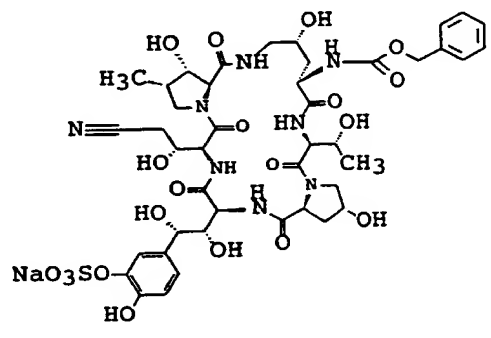
For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation form pressurized as powders which may be formulated and the powder compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

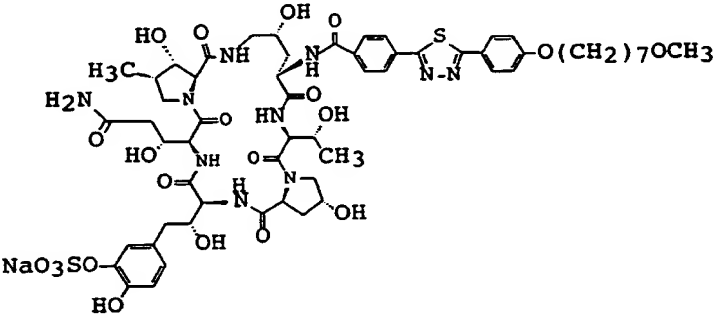
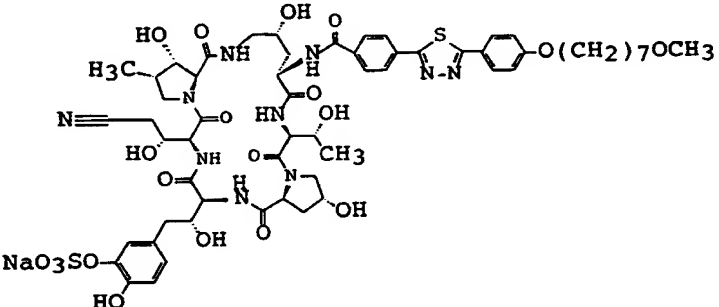
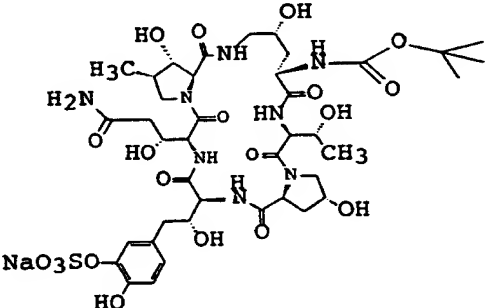
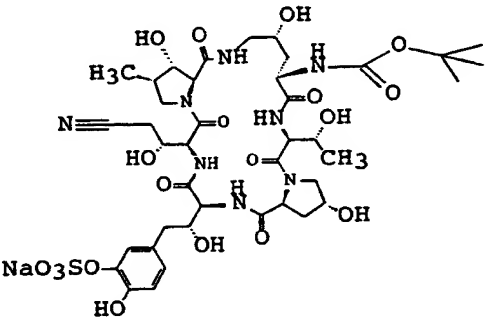
Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.

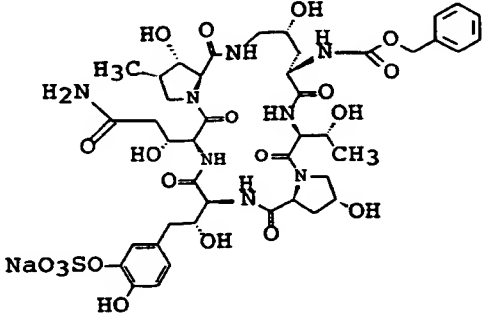
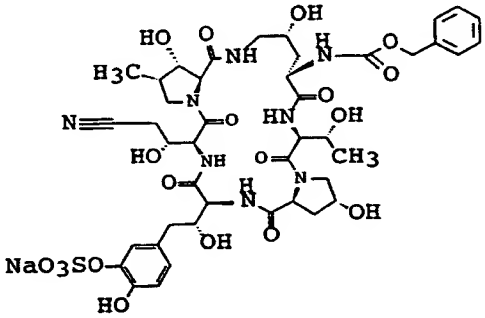
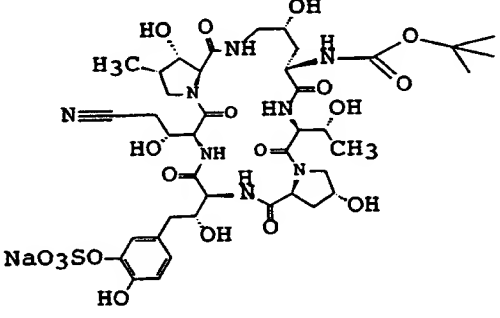
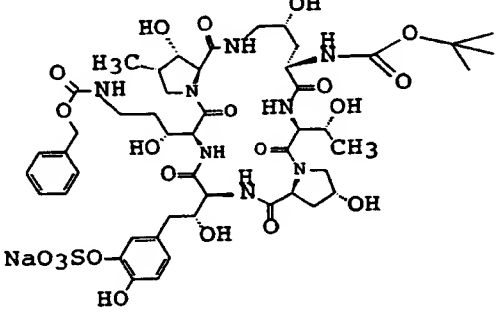
Alternatively, parenteral administration may be employed using drip intravenous administration.

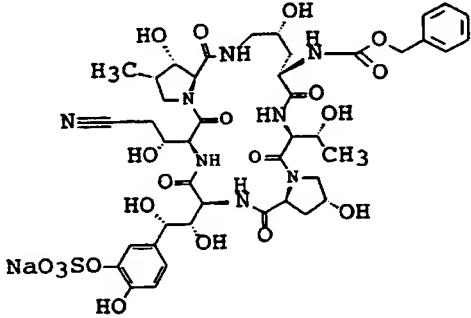
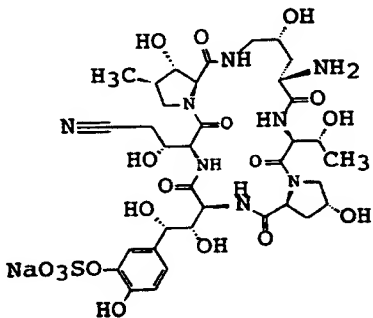
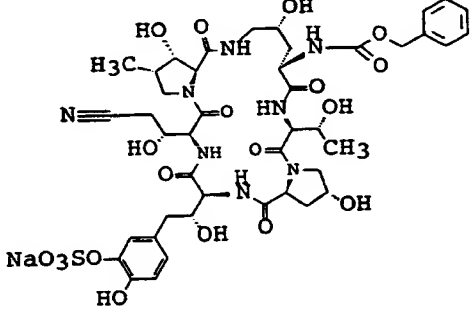
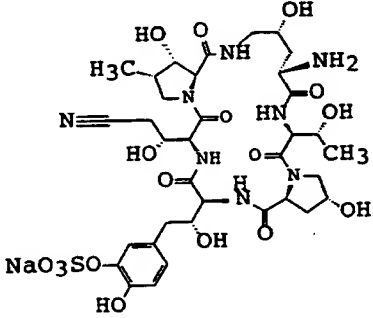
The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

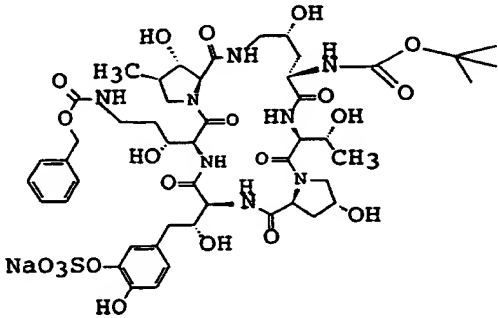
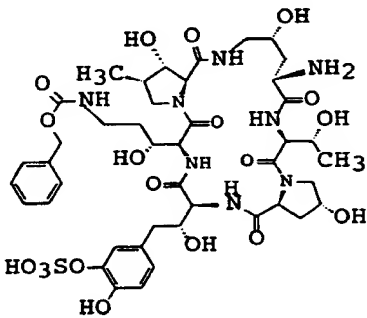
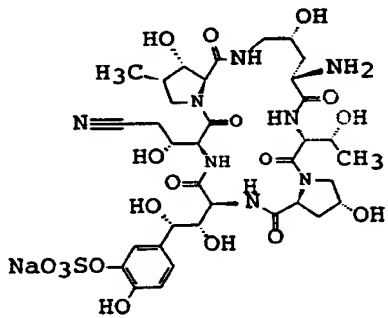
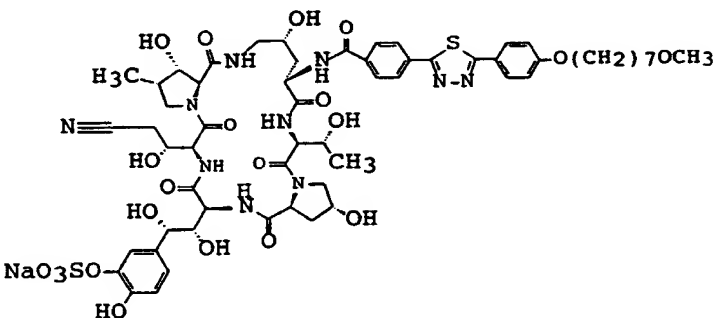
The Starting Compounds used and the Object Compounds obtained in the following Preparations 1 to 23 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

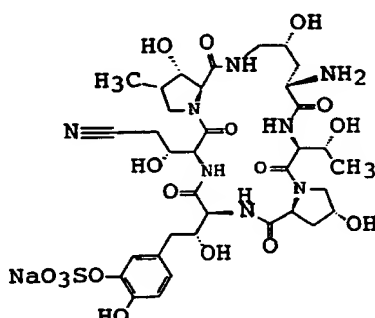
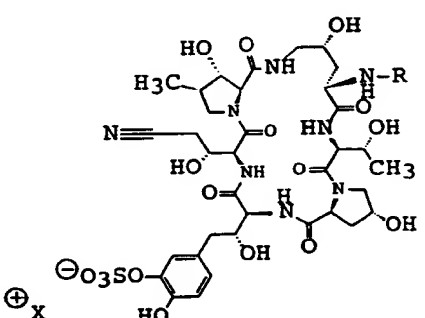
Preparation No.	Formula
1	 <p>Chemical structure of a complex molecule, likely a derivative of a natural product. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO₃SO-). The structure is highly branched and contains several nitrogen-containing rings.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different sulfonate group (NaO₃SO-) and a different amide bond configuration.</p>
2	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different sulfonate group (NaO₃SO-) and a different amide bond configuration.</p>
	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different sulfonate group (NaO₃SO-) and a different amide bond configuration.</p>

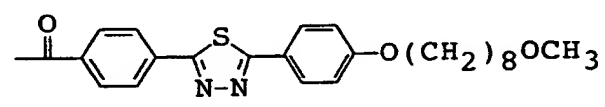
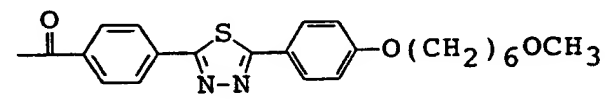
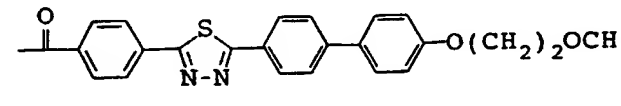
Preparation No.	Formula
3	
	
4	
	

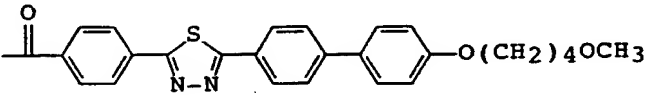
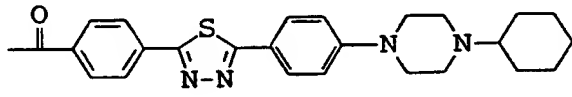
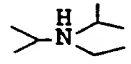
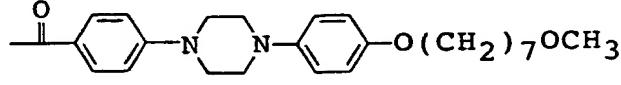
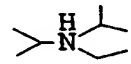
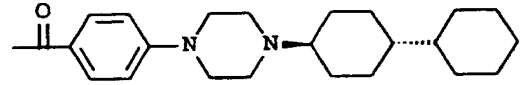
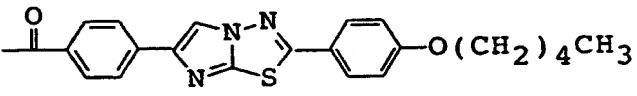
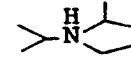
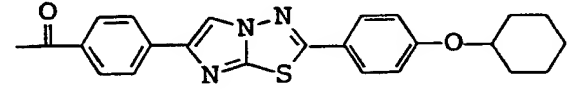
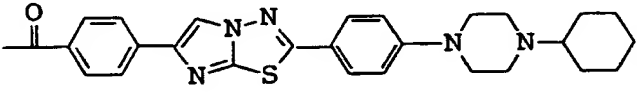
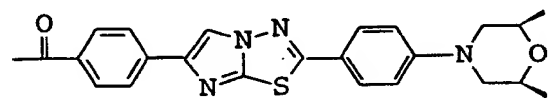
Preparation No.	Formula
5	
	
6	
	

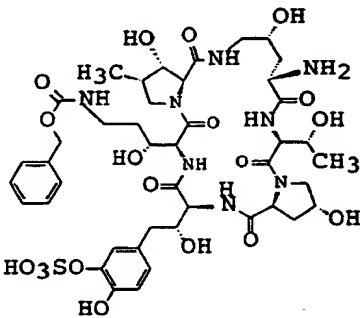
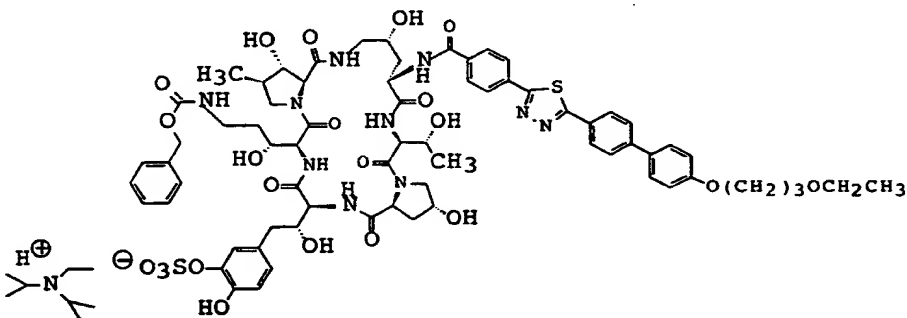
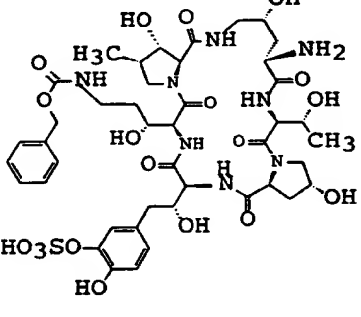
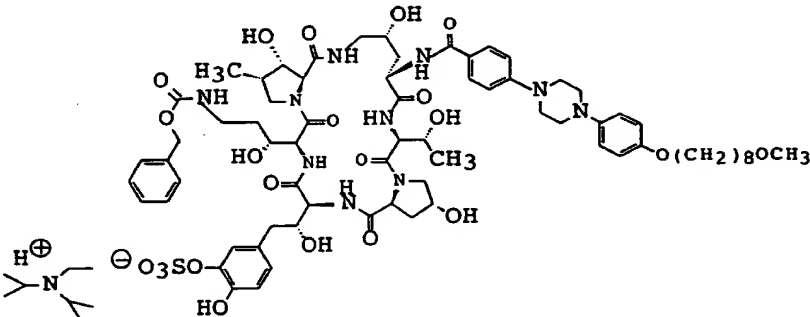
Preparation No.	Formula
7	
	
8	
	

Preparation No.	Formula
9	
	
10	
	

Preparation No.	Formula
11 { 21	
	

Preparation No.	R	X
11		Na
12		Na
13		Na

Preparation No.	R	X
14		Na
15		
16		
17		Na
18		
19		Na
20		Na
21		Na

Preparation No.	Formula
22	
	
23	
	

Preparation 1

A solution of starting compound (20 g) in 1,4-dioxane (100 ml) was treated with a solution of 1N-sodium hydroxide (44.2 ml) diluted to 100 ml with water, and to the stirred
5 mixture was added a solution of di-tert-butylidicarbonate (9.2 g) in 1,4-dioxane (50 ml) and then stirred for 2 hours at room temperature. 500 ml of pH 6.86 phosphate buffer and 100 ml ethyl acetate were added and the mixture was stirred and the organic layer discarded. The aqueous layer was adjusted
10 to pH 7.0 with 1N-hydrochloric acid then evaporated to remove organic solvent, filtered, and purified by ODS column chromatography eluting with aqueous methanol (5-15%). Object compound containing fractions were pooled, evaporated, and lyophilized to give object compound (19.61 g) as an amorphous
15 white powder.

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d, $J=5.5\text{Hz}$), 1.34 (9H, s), 1.40-2.50 (9H, m), 2.80-3.0 (1H, m), 3.4-4.5 (15H, m), 4.70-5.40 (8H, m), 6.60-7.05 (6H, m), 7.25-8.00 (5H, m), 8.71 (1H, s)

20 MASS (m/z): 1003.3 (M^+-1)

Preparation 2

A mixture of starting compound (500 mg), N,N-dimethylformamide (5 ml) and synthetic A-4 zeolite (500
25 mg, Wako Chemical) was treated with diisopropyl ethylamine (66 mg), followed by methanesulfonyl chloride (58.5 mg) dropwise. After 1 hour at room temperature, further diisopropyl ethylamine (66 mg) and methanesulfonyl chloride (58.5 mg) were added. After 1.5 hours, additional
30 diisopropylamine (66 mg) and methanesulfonyl chloride (58.5 mg) were added. After 1.5 hours, the mixture was filtered and the filtrate was poured into ethyl acetate. The precipitate was collected, washed with ethyl acetate and dried. The powder was dissolved in saturated sodium hydrogen
35 carbonate solution then purified by ODS column chromatography

(Daisogel SP-120 ODS Daiso) eluting with aqueous methanol (5-12.5%). Object compound-containing fractions were pooled, evaporated to remove methanol, and lyophilized to give object compound (210 mg) as an amorphous white powder.

5 IR (KBr): 2258.2, 1664.3, 1629.6, 1529.3, 1517.7,
1446.4, 1268.9 cm^{-1}

NMR (DMSO- d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.07 (3H, d, $J=5\text{Hz}$), 1.40-3.00 (9H, m), 3.10-4.50 (15H, m),
4.50-5.30 (10H, m), 5.66-5.69 (1H, m), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.82 (1H, d, $J=8\text{Hz}$), 7.05 (1H, d, $J=1.7\text{Hz}$), 7.33 (5H, s), 7.20-7.50 (3H, m), 7.6-7.7 (1H, m), 8.27 (1H, d, $J=8.3\text{Hz}$), 8.84 (1H, s)

MASS (m/z): 1081.3 ($M^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{43}\text{H}_{55}\text{N}_8\text{O}_{20}\text{SNa} \cdot 6\text{H}_2\text{O}$:

15 C 44.25, H 5.79, N 9.60

Found: C 44.30, H 5.79, N 9.48

The following compounds [Preparations 3 to 5] were obtained according to a similar manner to that of Preparation 2.

Preparation 3

IR (KBr): 2256.3, 1631.5, 1538.9, 1513.8, 1442.5,
1257.4 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, d, $J=5.5\text{Hz}$), 1.20-1.60 (8H, m), 1.65-3.05 (13H, m),
3.21 (3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.45-4.57 (16H, m), 4.70-5.30 (7H, m), 5.87 (1H, d, $J=6.1\text{Hz}$),
6.72 (1H, d, $J=8.2\text{Hz}$), 6.76-6.81 (1H, m), 6.98 (1H, d, $J=1.3\text{Hz}$), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.40-7.53 (2H, m), 7.79 (1H, br s), 7.98 (2H, d, $J=8.7\text{Hz}$), 8.10 (4H, s), 8.34 (1H, d, $J=7.9\text{Hz}$), 8.72 (1H, d, $J=5.7\text{Hz}$), 8.73 (1H, s)

MASS (m/z): 1293.4 ($M^+ - \text{Na}$)

35 Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{73}\text{N}_{10}\text{O}_{20}\text{SNa} \cdot 6\text{H}_2\text{O}$:

C 48.87, H 6.01, N 9.83

Found: C 48.69, H 6.09, N 9.70

Preparation 4

- 5 IR (KBr): 2256.3, 1666.2, 1631.5, 1535.1, 1515.8,
1448.3, 1442.5, 1272.8, 1251.6, 1166.7, 1083.8,
1047.2 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d,
 $J=5.1\text{Hz}$), 1.35 (9H, s), 1.50-3.00 (9H, m), 3.10-
10 4.50 (17H, m), 4.65-5.00 (5H, m), 5.15-5.17 (2H,
m), 5.70-5.90 (1H, m), 6.68-6.78 (2H, m), 6.86-6.96
(2H, m), 7.32 (1H, d, $J=8\text{Hz}$), 7.40-7.50 (1H, m),
7.70-7.80 (1H, m), 8.30-8.40 (1H, m), 8.72 (1H, s)
- MASS (m/z): 985.3 ($M^+-\text{Na}$)
- 15 Elemental Analysis Calcd. for $\text{C}_{40}\text{H}_{58}\text{N}_8\text{O}_{19}\text{SNa}\cdot 9\text{H}_2\text{O}$:
C 41.02, H 6.45, N 9.57
Found: C 41.35, H 6.42, N 9.61

Preparation 5

- 20 IR (KBr): 2256.3, 1668.1, 1648.8, 1631.5, 1538.9,
1513.8, 1454.1, 1267.0 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d,
 $J=5.2\text{Hz}$), 1.5-2.9 (10H, m), 3.2-4.5 (15H, m), 4.7-
5.2 (9H, m), 5.7-5.8 (1H, m), 6.60-6.78 (2H, m),
25 6.96 (1H, br s), 7.33 (5H, s), 7.2-7.5 (3H, m),
7.7-7.8 (1H, m), 8.3 (1H, d, $J=7.5\text{Hz}$), 8.73 (1H, br
s)
- MASS (m/z): 1065.2 ($M^++\text{Na}$)
- Elemental Analysis Calcd. for $\text{C}_{43}\text{H}_{55}\text{N}_8\text{O}_{19}\text{SNa}\cdot 7\text{H}_2\text{O}$:
30 C 44.18, H 5.95, N 9.58
Found: C 44.21, H 5.82, N 9.54

Preparation 6

- A solution of starting compound (2.0 g) in methanol (100
35 ml) - water (20 ml) was treated with cobalt(II) chloride

hexahydrate (1.89 g) and then stirred to give a pink solution. Sodium borohydride (1.5 g) was then added portionwise and then stirred for 1 hour at room temperature. The reaction mixture was filtered through a bed of celite, washing with methanol (100 ml) - water (30 ml) solution. The ice-cooled filtrate was then treated dropwise with a solution of benzyloxy carbonyl chloride (Z-chloride) (0.34 ml) in tetrahydrofuran (5 ml) and stirred for 1 hour at the same temperature. Ethyl acetate (50 ml) was added followed by water (200 ml) and after stirring ~ 5 minutes, the separated organic layer was discarded. The aqueous layer was adjusted to pH 8.8 and evaporated to remove organic solvent and then purified by ODS column chromatography, eluting with aqueous acetonitrile (10-30%). Object compound containing fractions were pooled, evaporated, and lyophilized to give object compound (1.61 g) as an amorphous white powder.

IR (KBr): 1666.2, 1631.5, 1517.7, 1444.4, 1267.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.00-1.15 (3H, m), 1.33 (9H, s), 1.35-2.10 (6H, m), 2.10-2.50 (4H, m), 2.80-3.30 (4H, m), 3.60-4.55 (12H, m), 4.60-4.90 (2H, m), 4.99 (2H, s), 4.50-5.30 (4H, m), 6.60-7.10 (4H, m), 7.33 (5H, s), 7.35-7.90 (3H, m), 8.72 (1H, br s)

MASS (m/z): 1123.3 (M^+-Na)

Elemental Analysis Calcd. for $C_{48}H_{67}N_8O_{21}SNa \cdot 6H_2O$:

C 45.93, H 6.34, N 8.93

Found: C 45.68, H 6.33, N 8.82

Preparation 7

A solution of starting compound (2.0 g) in methanol (30 ml) was treated with wet 10% palladium on carbon (1.5 g) and exposed to one atmosphere of hydrogen gas via balloon. After 5.5 hours, water (4 ml) was added and hydrogenation continued for a further 30 minutes. Methanol (100 ml) was added and the catalyst removed by filtration. The solution was

concentrated in vacuo to remove methanol and the aqueous residue lyophilized to give object compound (1.69 g) as a pink colored amorphous powder.

IR (KBr): 2256.3, 1648.8, 1631.5, 1538.9, 1515.8,
1440.6, 1083.8, 1047.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.9\text{Hz}$), 1.7-2.8 (10H, m), 3.0-4.5 (19H, m), 4.6-5.3 (6H, m), 5.85-6.0 (1H, m), 6.72 (1H, d, $J=8.2\text{Hz}$), 6.82 (1H, dd, $J=1.8$ and 8.4Hz), 7.06 (1H, d, $J=1.7\text{Hz}$), 7.32 (1H, d, $J=8.9\text{Hz}$), 7.44 (1H, d, $J=9.1\text{Hz}$), 7.6-7.8 (2H, m), 7.8-8.0 (1H, br s)

MASS (m/z): 901.2 ($\text{M}^+ - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{35}\text{H}_{49}\text{N}_8\text{O}_{18}\text{SNa} \cdot 6\text{H}_2\text{O}$:

C 40.70, H 5.95, N 10.85

Found: C 40.60, H 5.94, N 10.71

The following compound was obtained according to a similar manner to that of Preparation 7.

20 Preparation 8

IR (KBr): 2256.3, 1648.8, 1631.5, 1538.9, 1513.8,
1267.0, 1083.8, 1047.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.9\text{Hz}$), 1.7-2.1 (2H, m), 2.1-2.9 (7H, m), 3.1-4.6 (16H, m), 4.7-5.4 (6H, m), 6.1 (1H, br s), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.75 (1H, d, $J=8.2\text{Hz}$), 6.96 (1H, br s), 7.2-7.55 (2H, m), 7.6-7.9 (2H, m)

MASS (m/z): 885.3 ($\text{M}^+ - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{35}\text{H}_{49}\text{N}_8\text{O}_{17}\text{SNa} \cdot 6\text{H}_2\text{O}$:

C 41.34, H 6.05, N 11.02

Found: C 41.58, H 5.99, N 10.94

Preparation 9

A suspension of starting compound (1.6 g) in dichloromethane (41 ml) was stirred with cooling at 5°C and

treated with triethylsilane (1.1 ml), followed by trifluoroacetic acid (5.3 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, then poured into 450 ml of pH 6.86 phosphate buffer and adjusted to pH 8.5 with 4N-sodium hydroxide solution. Organic solvent was removed by evaporation and the remaining aqueous solution purified by ODS column chromatography, eluting with aqueous acetonitrile (5-20%). Object compound-containing fractions were pooled, evaporated, and lyophilized to give object compound (1.25 g) as an amorphous white powder.

IR (KBr): 1633.4, 1537.0, 1517.7, 1440.6, 1267.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, d, $J=5.8\text{Hz}$), 1.27 (2H, d, $J=6.6\text{Hz}$), 1.28-1.70 (2H, m), 1.75-2.45 (4H, m), 2.65-3.30 (5H, m), 3.50-4.50 (11H, m), 4.60-4.90 (2H, m), 5.00 (2H, s), 5.05-5.40 (5H, m), 6.70 (2H, d, $J=8.2\text{Hz}$), 6.76 (2H, d, $J=8.2\text{Hz}$), 6.96 (1H, s), 7.00-7.15 (1H, m), 7.34 (5H, s), 7.40-7.95 (3H, m), 8.60-8.90 (1H, m)

MASS (m/z): 1023.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{43}\text{H}_{60}\text{N}_8\text{O}_{19}\text{S}\cdot 6\text{H}_2\text{O}$:

C 45.58, H 6.40, N 9.89

Found: C 45.49, H 6.24, N 9.70

25 Preparation 10

A solution of starting compound (3 g) in N,N-dimethylformamide (60 ml) was treated with 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester (2.65 g) and diisopropylethylamine (0.564 ml) and stirred for 4 hours 20 minutes at room temperature. Ethyl acetate (1 l) was added and the resulting precipitate collected, washed with isopropyl ether, and dried to give object compound (5.62 g) as a crude powder, which was used directly in the next step without purification.

The following compounds [Preparations 11 to 17] were obtained according to a similar manner to that of Preparation 10.

5

Preparation 11

The object compound was used directly in the next reaction without purification.

10 Preparation 12

The object compound was used directly in the next reaction without purification.

Preparation 1315 MASS (m/z): 1299.3 ($M^+ - Na$)Preparation 14

The object compound was used directly in the next reaction without purification.

20

Preparation 15

The object compound was used directly in the next reaction without purification.

25 Preparation 16

The object compound was used directly in the next reaction without purification.

Preparation 1730 MASS (m/z): 1237.3 ($M^+ - Na$)Preparation 18

A mixture of 4-[2-(4-pentyloxyphenyl)imidazo[2,1-b]-[1,3,4]thiadiazol-6-yl]benzoic acid (1.44 g),

35 1-hydroxybenzotriazole (714 mg), diisopropyl ethylamine (0.58

ml) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (810 mg) in N,N-dimethylformamide (50 ml) was stirred 6 hours at room temperature, then treated with starting compound (2 g) and stirred overnight. Additional
5 N,N-dimethylformamide (20 ml) was added and stirring continued for a further 5.5 hours. The clear solution was poured into ethyl acetate (1 l) and the precipitate collected and washed with isopropyl ether and dried to give crude object compound (3.58 g), which was used directly in the next
10 step without purification.

The following compounds [Preparations 19 and 20] were obtained according to a similar manner to that of Preparation 18.

15

Preparation 19MASS (m/z): 1286.3 (M^+ -Na)Preparation 20

20

MASS (m/z): 1354.4 (M^+ -Na)

The following compound was obtained according to a similar manner to that of Preparation 18.

25

Preparation 21IR (KBr): 1648.8, 1631.5, 1537.0, 1513.8, 1456.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=7\text{Hz}$), 1.10 (3H, d, $J=5.6\text{Hz}$), 1.18 (6H, d, $J=6\text{Hz}$), 1.4-5.3 (38H, m), 5.88 (1H, d, $J=6\text{Hz}$), 6.71 (1H, d, $J=8\text{Hz}$), 6.75-6.80
30 (1H, m), 6.97 (1H, br s), 7.12 (2H, d, $J=9\text{Hz}$), 7.42 (1H, d, $J=7.6\text{Hz}$), 7.50 (1H, d, $J=9\text{Hz}$), 7.78 (2H, d, $J=8.8\text{Hz}$), 7.7-8.0 (1H, br s), 7.96 (4H, s), 8.32 (1H, d, $J=8\text{Hz}$), 8.50 (1H, d, $J=7.1\text{Hz}$), 8.72 (1H, s), 8.79 (1H, s)

35

MASS (m/z): 1301.4 (M^+ -Na)

The following compounds [Preparations 22 to 23] were obtained according to a similar manner to that of Preparation 10.

5

Preparation 22

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.6\text{Hz}$), 6.67 (1H, d, $J=6.9\text{Hz}$), 6.73-6.75 (1H, m), 6.96 (1H, br s), 7.07 (2H, d, $J=8.8\text{Hz}$), 7.32 (5H, s), 7.73 (2H, d, $J=8.7\text{Hz}$), 7.87 (2H, d, $J=8.5\text{Hz}$), 8.06-8.14 (6H, m), 8.72 (1H, s), 8.80 (1H, d, $J=7.1\text{Hz}$)

MASS (m/z): 1465.5 (M^+-Na)

10

Preparation 23

The object compound was used directly in the next reaction without purification.

15

Preparation 24

To a solution of 1-(tert-butoxycarbonyl)-4-hydroxypiperidine (6 g) in N,N-dimethylformamide (30 ml) was portionwise added sodium hydride (60%, 1.6 g) at 5°C with stirring. The mixture was stirred at room temperature for 0.5 hour and at 60°C for an hour. To the reaction mixture was added dropwise 1,4-dibromobutane (19 g) at 5°C with stirring. The mixture was stirred at room temperature for 4 hours and at 50°C for 2 hours. The reaction mixture was poured into ice-water and extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1). The organic layer was washed with saturated sodium chloride aqueous solution and dried over magnesium sulfate. The magnesium sulfate was filtered under reduced pressure, and the filtrate was concentrated under reduced pressure to give oil. The oil was subjected to column chromatography on silica gel (silica gel 60 F254, Merck) and eluted with a mixture of ethyl acetate and n-hexane (1:10-1:3). The fractions containing the

25

30

35

objective compound were combined and concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-4-[(4-bromo)butoxy]piperidine (1.5 g).

5 NMR (CDCl₃, δ): 1.41 (9H, s), 1.43-1.60 (2H, m), 1.65-1.80 (4H, m), 1.85-2.3 (2H, m), 3.02-3.20 (2H, m), 3.38-3.51 (4H, m), 3.68-3.80 (2H, m)
 MASS (m/z): 238 (M⁺-Boc-2)

Preparation 25

10 The mixture of 1-(tert-butoxycarbonyl)-4-[4-(bromo-butoxy)]piperidine (3 g) and 28% sodium methoxide in methanol solution (20 ml) in methanol (50 ml) was refluxed for 8.5 hours with stirring. The reaction mixture was concentrated under reduced pressure, added water to the residue and
15 adjusted to pH 4 using the hydrochloric acid. The mixture was extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1), washed with saturated sodium chloride aqueous solution and dried over magnesium sulfate. The magnesium sulfate was filtered by suction, and the filtrate
20 was concentrated under reduced pressure to give an oil. The oil was subjected to column chromatography on silica gel (silica gel 60 F254, Merck) and eluted with a mixture of ethyl acetate and n-hexane (1:5-1:3). The fractions containing the objective compound were combined and
25 concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-4-(4-methoxybutoxy)piperidine (2.2 g).

 NMR (CDCl₃, δ): 1.40 (9H, s), 1.43-1.60 (2H, m), 1.6-1.70 (4H, m), 1.76-1.85 (2H, m), 3.01-3.15 (2H, m), 3.33 (3H, s), 3.36-3.50 (5H, m), 3.69-3.80 (2H, m)
30 MASS (m/z): 188 (M⁺-Boc+1)

Preparation 26

 To a mixture of 1-(tert-butoxycarbonyl)-4-[4-methoxybutoxy]piperidine (2.2 g) and anisole (5 ml) in
35

dichloromethane (10 ml) was added dropwise trifluoroacetic acid (10 ml) at 5°C with stirring. The mixture was stirred at room temperature for 3 hours and evaporated to dryness in vacuo at 70°C to give an oil (2.5 g). The mixture of the
5 above oil (2.5 g), 4-fluorobenzonitrile (1.5 g) and potassium carbonate (3 g) in dimethylsulfoxide (25 ml) was heated at 160°C for 3 hours with stirring. The reaction mixture was poured into ice-water and extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1). The organic layer was
10 separated, washed with saturated sodium chloride aqueous solution and dried over magnesium sulfate. The magnesium sulfate was filtered by suction and the filtrate was concentrated under reduced pressure to give solid. The solid was subjected to column chromatography on silica gel (silica
15 gel 60 F₂₅₄, Merck) and eluted first a mixture of ethyl acetate and n-hexane (1:5), second a mixture of dichloromethane and methanol (10:1). The fractions containing the objective compound were combined and concentrated under reduced pressure to give 4-[4-(4-methoxybutoxy)piperidin-1-yl]benzonitrile (2.0 g).
20

NMR (CDCl₃, δ): 1.58-1.76 (6H, m), 1.89-2.00 (2H, m),
3.08-3.21 (2H, m), 3.33 (3H, s), 3.37-3.68 (7H, m),
6.85 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz)

MASS (m/z) (API-ES-Positive): 312 (M⁺+Na+1)

25

Preparation 27

The mixture of 4-[4-(4-methoxybutoxy)piperidin-1-yl]benzonitrile (2 g), thiosemicarbazide (1 g) and trifluoroacetic acid (10 ml) in toluene (20 ml) was stirred
30 at 60-65°C for 9 hours. The reaction mixture was poured into ice-water and adjusted to pH 9 using sodium hydroxide aqueous solution. The mixture was extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1), washed with saturated sodium chloride aqueous solution and dried over magnesium
35 sulfate. The magnesium sulfate was filtered by suction, the

filtrate was concentrated under reduced pressure and the residue was triturated with isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give 2-amino-5-[4-(4-methoxybutoxy)piperidin-1-yl]phenyl][1,3,4]thiadiazole (2.0 g).

NMR (DMSO- d_6 , δ): 1.40-1.60 (6H, m), 1.80-2.00 (2H, m), 2.86-3.15 (2H, m), 3.23 (3H, s), 3.30-3.50 (5H, m), 3.50-3.61 (2H, m), 6.98 (2H, d, $J=8.9\text{Hz}$), 7.19 (2H, s), 7.54 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 363 ($M^+ + 1$)

Preparation 28

A mixture of 2-amino-5-[4-(4-methoxybutoxy)piperidin-1-yl]phenyl[1,3,4]thiadiazole (2 g) and 4-(ethoxycarbonyl)phenacylbromide (2.3 g) in ethanol (25 ml) was refluxed for 6 hours with stirring. After cooling, the reaction mixture was poured into isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give solid. The mixture of this solid and trifluoroacetic acid (10 ml) in xylene (60 ml) was heated at 130°C for 6 hours with stirring. The reaction mixture was concentrated under reduced pressure and the residue was triturated with isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give ethyl-4-[2-[4-(4-methoxybutoxypiperidin-1-yl)phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoate (2.4 g).

IR (KBr): 2939, 2854, 1708, 1604, 1469 cm^{-1}

NMR (DMSO- d_6 , δ): 1.34 (3H, t, $J=7.2\text{Hz}$), 1.40-1.65 (6H, m), 1.75-1.95 (4H, m), 3.00-3.20 (2H, m), 3.22 (3H, s), 3.25-3.40 (2H, m), 3.40-3.90 (3H, m), 4.33 (2H, q, $J=7.5\text{Hz}$), 7.02 (2H, d, $J=8.8\text{Hz}$), 7.57 (2H, d, $J=8.8\text{Hz}$), 7.75 (2H, d, $J=8.8\text{Hz}$), 8.00 (1H, s), 8.14 (2H, d, $J=9.0\text{Hz}$)

MASS (m/z): 535 ($M^+ + 1$)

Preparation 29

A solution of ethyl-4-[2-4-[4-methoxybutoxypiperidin-1-yl)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoate (2.4 g) and 10% sodium hydroxide aqueous solution (15 ml) in methanol (50 ml) and tetrahydrofuran (25 ml) was refluxed for 6 hours with stirring. The reaction mixture was concentrated under reduced pressure, ice-water was added to the residue and adjusted to pH 3 using hydrochloric acid. The mixture was shaken with a mixture of ethyl acetate and tetrahydrofuran (1:1). The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-[2-[4-(4-methoxybutoxy)piperidin-1-yl-phenyl]imidazo[2,1-b]-[1,3,4]thiadiazol-6-yl]benzoic acid (2 g).

IR (KBr): 2854, 2650, 2550, 1691, 1678, 1608, 1599, 1476 cm^{-1}

NMR (DMSO- d_6 , δ): 1.20-1.60 (6H, m), 1.60-2.05 (2H, m), 3.00-3.30 (2H, m), 3.22 (3H, m), 3.00-4.00 (7H, m), 7.10 (2H, d, $J=8.8\text{Hz}$), 7.75 (2H, d, $J=8.7\text{Hz}$), 7.99 (4H, m), 8.81 (1H, s), 12.90 (1H, br s)

MASS (m/z): 507 ($M^+ + 1$)

Preparation 30

To a solution of 4-[2-[4-(4-methoxybutoxypiperidin-1-yl)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (2.4 g) in dichloromethane (150 ml) was added triethylamine (1.3 g), 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (2 g) and 1-hydroxybenzotriazole (1 g). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was triturated with water. The precipitates were collected by filtration, washed with water and isopropyl ether and dried in vacuo to give 4-[2-[4-(4-methoxybutoxy)piperidin-1-yl-phenyl]imidazo[2,1-

b][1,3,4]thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester
(2.5 g).

IR (KBr): 3427, 2937, 2856, 1774, 1602, 1471 cm^{-1}

NMR (DMSO-d_6 , δ): 1.30-1.65 (6H, m), 1.70-2.10 (2H, m),
5 3.21 (3H, m), 2.80-3.60 (7H, m), 3.60-3.80 (2H, m),
7.05-8.00 (10H, m), 8.00 (1H, s), 8.21 (1H, d,
J=8.6Hz), 8.33 (1H, d, J=8.6Hz)

MASS (m/z): 624 ($\text{M}^+ + 1$)

10 The following compound was obtained according to a
similar manner to that of Preparation 26.

Preparation 31

4-(3-Methoxypropoxypiperidin-1-yl)benzonitrile

15 IR (KBr): 2931, 2866, 2215, 1678, 1604, 1516 cm^{-1}

NMR (DMSO-d_6 , δ): 1.35-1.60 (2H, m), 1.60-1.80 (2H, m),
1.80-2.00 (2H, m), 2.86-3.25 (2H, m), 3.21 (3H, s),
3.30-3.60 (5H, m), 3.60-3.80 (2H, m), 7.01 (2H, d,
J=9Hz), 7.55 (2H, d, J=8.9Hz)

20 MASS (m/z): 275 ($\text{M}^+ + 1$)

The following compound was obtained according to a
similar manner to that of Preparation 27.

25 Preparation 32

2-Amino-5-[4-(3-methoxypropoxypiperidin-1-yl)phenyl]-
[1,3,4]thiadiazole

NMR (DMSO-d_6 , δ): 1.30-1.60 (2H, m), 1.65-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.20 (2H, m), 3.21 (3H, s),
30 3.30-3.70 (7H, m), 6.98 (2H, d, J=8.9Hz), 7.19 (2H,
br s), 7.54 (2H, d, J=8.8Hz)

MASS (m/z): 349 ($\text{M}^+ + 1$)

The following compound was obtained according to a
35 similar manner to that of Preparation 28.

Preparation 33

Ethyl-4-[2-[4-(3-methoxypropoxypiperidin-1-yl)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoate

5 IR (KBr): 3411, 3211, 3132, 2943, 2862, 1709, 1604 cm^{-1}

NMR (DMSO- d_6 , δ): 1.30-1.60 (5H, m), 1.65-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.10 (2H, m), 3.22 (3H, s),
3.30-3.80 (6H, m), 4.20-4.50 (3H, m), 6.98 (2H, d,
J=9Hz), 7.40 (1H, s), 7.54 (2H, d, J=8.8Hz), 7.80-
10 8.40 (4H, m)

MASS (m/z): 521 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 29.

15

Preparation 34

4-[2-[4-(3-Methoxypropoxypiperidin-1-yl)phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid

20 IR (KBr): 3423, 2935, 2858, 2650, 2550, 1682, 1603, 1468 cm^{-1}

NMR (DMSO- d_6 , δ): 1.40-1.60 (2H, m), 1.60-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.20 (2H, m), 3.22 (3H, s),
3.30-3.80 (7H, m), 6.98 (2H, d, J=8.7Hz), 7.19 (1H, s),
7.54 (2H, d, J=8.7Hz), 7.80-8.20 (4H, m)

25 MASS (m/z): 493 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 30.

30 Preparation 35

4-[2-[4-(3-Methoxypropoxypiperidin-1-yl)phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
benzotriazol-1-yl ester

35 IR (KBr): 3464, 3429, 3425, 3402, 2932, 2931, 1774, 1605, 1469 cm^{-1}

NMR (DMSO- d_6 , δ): 1.30-1.60 (2H, m), 1.60-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.30 (2H, m), 3.22 (3H, s),
3.35-3.80 (7H, m), 7.08 (2H, d, $J=9.1\text{Hz}$), 7.20-8.00
(8H, m), 8.00 (1H, s), 8.14 (1H, d, $J=8.6\text{Hz}$), 8.33
(1H, d, $J=8.5\text{Hz}$)

MASS (m/z): 610 ($M^+ + 1$)

Preparation 36

A mixture of methyl 4-methylsulfinylbenzoate (6.0 g),
sodium acetate (11 g) and acetic anhydride (60 ml) was
stirred for 7.5 hours at 180°C . The reaction mixture was
cooled and filtered by suction. The filtrate was
concentrated under reduced pressure and the residue was
trituated with water. The precipitates were collected by
filtration, washed with aqueous sodium carbonate and water.
The solid was subjected to column chromatography on silica
gel (silica gel 60 F254, Merck: 200 g) and eluted with a
mixture of ethyl acetate and toluene (1:5). The fractions
containing the objective compound were combined and
concentrated under reduced pressure to give methyl 4-
acetoxymethylthiobenzoate (5.5 g).

IR (KBr): 1746, 1704, 1593 cm^{-1}

NMR (CDCl_3 , δ): 2.12 (3H, s), 3.92 (3H, s), 5.50 (2H,
s), 7.63 (2H, d, $J=8.3\text{Hz}$), 7.98 (2H, d, $J=8.3\text{Hz}$)

MASS (m/z) (API-ES-Positive): 263 ($M^+ + 23$)

Preparation 37

To a solution of methyl 4-acetoxymethylthiobenzoate
(15.5 g) in a mixture of methanol (20 ml) and dichloromethane
(60 ml) was portionwise added magnesium monoperoxyphthalate
hexahydrate (24 g) at 5°C , with stirring. The mixture was
stirred at room temperature for 2 hours. The reaction
mixture was washed with ice-water, aqueous sodium carbonate
and brine, then dried over magnesium sulfate. The organic
solvent was concentrated under reduced pressure to give

acetoxymethyl-(4-methoxycarbonylphenyl)-
sulfone (5.9 g).

IR (KBr): 1759, 1724, 1434 cm^{-1}

5 NMR (CDCl_3 , δ): 2.09 (3H, s), 3.98 (3H, s), 5.18 (2H, s), 8.01 (2H, d, $J=8.5\text{Hz}$), 8.26 (2H, d, $J=8.5\text{Hz}$)

MASS (m/z): 273 (M^++1)

Preparation 38

To a solution of methyl 4-acetoxymethylsulfonyl-
10 benzoate (5.5 g) in a mixture of tetrahydrofuran (50 ml) and
methanol (25 ml) was added dropwise 10% aqueous sodium
hydroxide at 5°C with stirring. The mixture was stirred at
room temperature for 3 hours. The reaction mixture was
concentrated under reduced pressure and to the residue was
15 added water. The solution was washed with toluene and the
aqueous layer was concentrated under reduced pressure and
dried in vacuo at 50°C to give sodium
methoxycarbonylbenzenesulfinate (4.5 g).

IR (KBr): 3424, 3300, 1718, 1594 cm^{-1}

20 NMR ($\text{DMSO}-d_6$, δ): 3.84 (3H, s), 7.60 (2H, d, $J=8.0\text{Hz}$),
7.92 (2H, d, $J=8.0\text{Hz}$)

MASS (m/z) (API-ES-Positive): 245 (M^++23)

Preparation 39

25 A mixture of sodium-4-(1-methoxycarbonyl)benzene
sulfinate (2.2 g) and 1,7-dibromoheptane (2.6 g) in N,N-
dimethylformamide (50 ml) was stirred at 100°C for 5 hours.
The reaction mixture was concentrated under reduced pressure
and the residue was triturated with water. The mixture was
30 extracted with a mixture of ethyl acetate and tetrahydrofuran
(1:1), washed with brine and dried over magnesium sulfate.
After removing the magnesium sulfate, the filtrate was
concentrated under reduced pressure to give a yellow oil. The
oily product was subjected to column chromatography on silica
35 gel (silica gel 60 F254, Merck: 250 g) and eluted with a

mixture of ethyl acetate and toluene (1:10). The fractions containing the objective compound were combined and concentrated under reduced pressure to give 7-bromoheptyl-[4-(methoxycarbonyl)phenyl]sulfone (1.4 g).

5 IR (Neat): 3423, 2927, 2852, 1725, 1280 cm^{-1}
NMR (CDCl_3 , δ): 1.20-1.43 (6H, m), 1.60-1.85 (4H, m),
3.11 (2H, m), 3.38 (2H, t, $J=6.7\text{Hz}$), 3.98 (3H, s),
8.00 (2H, d, $J=8.4\text{Hz}$), 8.23 (2H, d, $J=8.4\text{Hz}$)
MASS (m/z): 379 (M^+)

10

Preparation 40

A mixture of 7-bromoheptyl-[4-(methoxycarbonyl)-phenyl]sulfone (1.4 g) and sodium methoxide in methanol solution (28%) (2 ml) in methanol (20ml) was refluxed for 10
15 hours with stirring. The reaction mixture was concentrated under reduced pressure and subjected to column chromatography on silica gel (silica gel 60 F254, Merck) and eluted with a mixture of ethyl acetate and toluene (1:5-1:3). The fractions containing the objective compound were combined and
20 concentrated under reduced pressure to give 7-methoxyheptyl-[4-(methoxycarbonyl)phenyl]sulfone (0.85 g).

IR (Neat): 2929, 2857, 1723, 1280 cm^{-1}
NMR (CDCl_3 , δ): 3.15-3.40 (8H, m), 3.40-3.80 (4H, m),
3.98 (3H, s), 8.00 (2H, d, $J=8.5\text{Hz}$), 8.23 (2H, d,
25 $J=8.5\text{Hz}$)
MASS (m/z): 328 (M^++1)

Preparation 41

A mixture of 7-methoxyheptyl-[4-(methoxycarbonyl)-phenyl]sulfone (0.85 g) and 1N-aqueous sodium hydroxide (5
30 ml) in a mixture of ethanol (20 ml) and tetrahydrofuran (10 ml) was stirred at 80°C for 5 hours. The reaction mixture was concentrated under reduced pressure and the residue was triturated with water. The solution was adjusted to pH 1.0
35 using diluted hydrochloric acid. The precipitates were

collected by filtration, washed with water and dried in vacuo to give 7-methoxyheptyl-(4-carboxyphenyl)sulfone (0.8 g) white solid.

IR (KBr): 2674, 2555, 1698, 1425, 1285 cm^{-1}

5 NMR ($\text{DMSO}-d_6$, δ): 1.1-1.4 (6H, m), 1.40-1.60 (4H, m),
3.21 (3H, s), 3.18-3.40 (4H, m), 8.00 (2H, d,
 $J=8.5\text{Hz}$), 8.18 (2H, d, $J=8.5\text{Hz}$)

MASS (m/z): 315 (M^++1)

10 Preparation 42

A mixture of 7-methoxyheptyl-4-carboxyphenyl-sulfone (0.8 g) and thionyl chloride (10 ml) was refluxed for 2 hours with stirring. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in
15 tetrahydrofuran (10 ml). To a mixture of 4-(methoxycarbonyl)benzamide oxime (0.49 g) in pyridine (25 ml) was added dropwise the above acid chloride solution at 5°C with stirring. The mixture was stirred at 5°C for 0.5 hour and continued at room temperature for an hour. The reaction
20 mixture was concentrated under reduced pressure and the residue was triturated with water. The precipitates were collected by filtration, washed with water and dried to give 4-(methoxycarbonyl)-O-4'-[(7-methoxyheptylsulfonyl)-benzoyl]benzamide oxime (1.0 g).

25 IR (KBr): 3492, 3369, 2933, 2857, 1724, 1616, 1276 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.15-1.54 (12H, m), 3.23 (3H, s),
3.22-3.40 (2H, m), 3.90 (3H, s), 7.25 (2H, br s),
7.95 (2H, d, $J=8.3\text{Hz}$), 8.00-8.17 (4H, m), 8.47 (2H,
d, $J=8.3\text{Hz}$)

30 MASS (m/z): 491 (M^++1)

Preparation 43

A solution of 4-methoxycarbonyl-O-[4'-(7-methoxyheptylsulfonyl)benzoyl]benzamide oxime (1.0 g) in N,N-
35 dimethylformamide (10 ml) was stirred at 100°C for 6 hours.

The reaction mixture was poured into ice-water and adjusted to pH 1 using diluted hydrochloric acid. The precipitates were collected by filtration, washed with water and dried to give methyl-4-[5-[4-(7-methoxyheptyl-

5 sulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoate (0.82 g).

IR (KBr): 2931, 2857, 1724, 1280 cm^{-1}

NMR (DMSO-d_6 , δ): 1.20-1.60 (10H, m), 3.17 (3H, s),
3.22-3.43 (4H, m), 3.92 (3H, s), 8.17-8.30 (6H, m),
8.47 (2H, d, $J=8.3\text{Hz}$)

10 MASS (m/z): 473 (M^++1)

Preparation 44

A mixture of methyl 4-[5-[4-(7-methoxyheptylsulfonyl)phenyl]-1,2,4-oxazol-3-yl]benzoate (0.8
15 g) and 10% sodium hydroxide aqueous solution (2 ml) in a mixture of ethanol (25 ml) and tetrahydrofuran (10 ml) was refluxed for 3.5 hours with stirring. The reaction mixture was concentrated under reduced pressure and to the residue was added water and adjusted to pH 1 using diluted
20 hydrochloric acid. The precipitates were collected by filtration, washed with water and dried to give 4-[5-[4-(7-methoxyheptylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid (0.8 g).

IR (KBr): 2931, 2857, 2750, 2650, 1693, 1415 cm^{-1}

25 NMR (DMSO-d_6 , δ): 1.15-1.60 (10H, m), 3.18 (3H, s),
3.20-3.50 (4H, m), 8.16-8.30 (6H, m), 8.47 (2H, d,
 $J=8.4\text{Hz}$)

MASS (m/z): 459 (M^++1)

30 Preparation 45

To a solution of 4-[5-[4-(7-methoxyheptylsulfonyl)-phenyl]-1,2,4-oxazol-3-yl]benzoic acid (0.8 g) and triethylamine (0.4 g) in dichloromethane (30 ml) was added 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (0.7 g) and 1-
35 hydroxybenzotriazole (0.36 g). The mixture was stirred at

room temperature for 8 hours. The reaction mixture was washed with water, saturated sodium chloride aqueous solution and dried over magnesium sulfate. After magnesium sulfate was filtered off, the filtrate was concentrated under reduced pressure and the residue was triturated with isopropyl ether.

The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give 4-[5-[4-(7-methoxyheptylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester (0.89 g).

10 IR (KBr): 2931, 2857, 1787, 1616, 1409, 1282 cm^{-1}

NMR (DMSO-d_6 , δ): 1.10-1.50 (10H, m), 3.18 (3H, s),
3.22-3.40 (4H, m), 7.25-7.60 (2H, m), 7.70 (1H, d,
J=8.5Hz), 7.96 (1H, d, J=8.5Hz), 8.19-8.24 (6H, m),
8.47 (2H, d, J=8.3Hz)

15 MASS (m/z): 576 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 39.

20 Preparation 46

1-[4-(Methoxycarbonyl)phenylsulfonyl]-9-bromoheptane

IR (KBr): 2925, 2850, 1724, 1461, 1280 cm^{-1}

25 NMR (DMSO-d_6 , δ): 1.10-1.35 (10H, m), 1.40-1.55 (2H, m),
1.60-1.80 (2H, m), 3.33-3.41 (2H, m), 3.50 (2H, t,
J=6.7Hz), 3.91 (3H, s), 8.05 (2H, d, J=8.4Hz), 8.20
(2H, d, J=8.4Hz)

MASS (m/z): 405 (M^+)

30 The following compound was obtained according to a similar manner to that of Preparation 40.

Preparation 47

1-[4-(Methoxycarbonyl)phenyl]sulfonyl-9-methoxyheptane

IR (KBr): 2927, 2854, 1699, 1425, 1286 cm^{-1}

35 NMR (DMSO-d_6 , δ): 1.10-1.30 (10H, m), 1.30-1.48 (6H, m),

3.19 (3H, s), 3.23-3.39 (4H, m), 3.90 (3H, s), 8.01 (2H, d, J=8.3Hz), 8.17 (2H, d, J=8.3Hz)

MASS (m/z): 357 (M^+ +1)

- 5 The following compound was obtained according to a similar manner to that of Preparation 41.

Preparation 48

1-[4-Carboxyphenylsulfonyl]-9-methoxyheptane

10 IR (KBr): 2937, 2852, 2672, 2550, 1698, 1425, 1320, 1286 cm^{-1}

NMR (DMSO- d_6 , δ): 1.10-1.30 (10H, m), 1.40-1.47 (4H, m), 3.19 (3H, s), 3.23-3.39 (3H, m), 8.01 (2H, d, J=8.3Hz), 8.17 (2H, d, J=8.3Hz)

15 MASS (m/z): 343 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparations 42 and 43.

20 Preparation 49

Methyl 4-[5-[4-(9-methoxy-n-nonylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoate

IR (KBr): 2925, 2854, 1724, 1612, 1409, 1278 cm^{-1}

25 NMR (DMSO- d_6 , δ): 1.19-1.57 (14H, m), 3.17 (3H, s), 3.12-3.43 (4H, m), 3.92 (3H, s), 8.17-8.30 (6H, m), 8.47 (2H, d, J=8.4Hz)

MASS (m/z): 501 (M^+ +1)

- 30 The following compound was obtained according to a similar manner to that of Preparation 44.

Preparation 50

4-[5-[4'-(9-Methoxy-n-nonylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid

35 IR (KBr): 2927, 2854, 2667, 2550, 1691, 1614, 1415,

1282 cm^{-1}

NMR (DMSO-d_6 , δ): 1.10-1.30 (10H, m), 1.30-1.60 (4H, m),
3.17 (3H, s), 3.19-3.46 (4H, m), 8.00-8.27 (6H, m),
8.47 (2H, d, $J=8.3\text{Hz}$), 13.34 (1H, br s)

5 MASS (m/z): 487 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 45.

10 Preparation 51

4-[5-[4-(9-Methoxy-n-nonylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 2927, 2854, 1785, 1614, 1411, 1282 cm^{-1}

15 NMR (DMSO-d_6 , δ): 1.10-1.30 (10H, m), 1.30-1.60 (4H, m),
3.17 (3H, s), 3.03-3.43 (4H, m), 7.36-7.58 (2H, m),
7.72 (1H, d, $J=8.3\text{Hz}$), 7.98 (1H, d, $J=8.3\text{Hz}$), 8.17-
8.27 (6H, m), 8.47 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 604 (M^++1)

20 Preparation 52

To a mixture of methyl 4-hydroxybenzoate (1.52 g) and potassium carbonate (0.76 g) in acetone (30 ml) was added dropwise a solution of 1,7-dibromoheptane (3.1 g) in acetone (10 ml) at room temperature with stirring. The mixture was
25 stirred at room temperature for 2.5 hours, and then refluxed for overnight with stirring. The reaction mixture was filtered under reduced pressure and the filtrate was concentrated under reduced pressure to give an oily solid. The oily solid was subjected to column chromatography on
30 silica gel (silica gel 60 F254, Merck: 200 g) and eluted with a mixture of ethyl acetate and n-hexane (1:3). The fractions containing the objective compound were combined and concentrated under reduced pressure to give methyl 4-(7-bromo-n-heptyloxy]benzoate (2.3 g).

35 NMR (CDCl_3 , δ): 1.43-1.60 (6H, m), 1.74-1.90 (4H, m),

3.42 (2H, t, J=6.8Hz), 3.88 (3H, s), 4.00 (2H, t, J=6.8Hz), 6.89 (2H, d, J=8.9Hz), 7.98 (2H, d, J=8.9Hz)

MASS (m/z)(API-ES-Positive): 329 (M^+)

5

Preparation 53

A solution of methyl 4-[7-bromo-n-heptyloxy]benzoate (2.3 g) in methanol (50 ml) and a solution of 28% sodium methoxide in methanol (3.5 ml) was refluxed for 12 hours with stirring. The reaction mixture was concentrated under reduced pressure and water was added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give an oil. The oil was subjected to column chromatography on silica gel (silica gel 60 F254, Merck: 100 g) and eluted with a mixture of ethyl acetate and n-hexane (1:5). The fractions containing the objective compound were combined and concentrated under reduced pressure to give methyl 4-(7-methoxyheptyloxy)benzoate (1.6 g) as an oil.

IR (Neat): 2937, 2867, 1718, 1607, 1469, 1442 cm^{-1}
NMR (CDCl_3 , δ): 1.15-1.60 (8H, m), 1.60-1.84 (2H, m), 3.33 (3H, s), 3.30-3.40 (2H, t, J=6.4Hz), 3.88 (3H, s), 4.00 (2H, t, J=6.4Hz), 6.92 (2H, d, J=8.8Hz), 8.00 (2H, d, J=8.8Hz)

MASS (m/z): 281 ($M^+ + 1$)

Preparation 54

A mixture of methyl 4-(7-methoxy-n-heptyloxy)benzoate (1.5 g) and 1N-sodium hydroxide aqueous solution in ethanol (10 ml) and tetrahydrofuran (10 ml) was heated at 40-60°C for 5 hours with stirring. The reaction mixture was concentrated under reduced pressure and water added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-[7-methoxy-n-heptyloxy]benzoic acid (1.4 g)

as a white solid.

IR (KBr): 2937, 2857, 2665, 2561, 1691, 1666, 1606,
1428 cm^{-1}

5 NMR (DMSO-d_6 , δ): 1.20-1.55 (8H, m), 1.60-1.80 (2H, m),
3.20 (3H, s), 3.29 (2H, d, $J=6.4\text{Hz}$), 4.03 (2H, d,
 $J=6.4\text{Hz}$), 7.00 (2H, d, $J=8.7\text{Hz}$), 7.87 (2H, d,
 $J=8.7\text{Hz}$)

MASS (m/z)(API-ES-Positive): 289 (M^++23), 249

10 Preparation 55

A mixture of 4-(7-methoxy-n-heptyloxy)benzoic acid (4 g) and thionyl chloride (40 ml) was refluxed for 2 hours with stirring. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in
15 tetrahydrofuran (40 ml). To a mixture of 4-(methoxycarbonyl)benzamide oxime (2.8 g) in pyridine (30 ml) was added dropwise the above acid chloride solution at 5°C with stirring. The mixture was stirred at 5°C for 0.5 hour and continued at room temperature for 0.5 hour. The reaction
20 mixture was poured into water. The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-(methoxycarbonyl)-O-[4-(7-methoxy-n-heptyloxy)benzoyl]benzamide oxime (6.0 g).

IR (KBr): 3478, 3372, 2931, 2854, 1714, 1605 cm^{-1}

25 NMR (DMSO-d_6 , δ): 1.20-1.55 (8H, m), 1.60-1.80 (2H, m),
3.21 (3H, s), 3.30 (3H, t, $J=6.4\text{Hz}$), 3.89 (3H, s),
4.07 (2H, t, $J=6.4\text{Hz}$), 7.03 (2H, d, $J=8.4\text{Hz}$), 7.08
(2H, br s), 7.92 (2H, d, $J=8.4\text{Hz}$), 8.05 (2H, d,
 $J=8.4\text{Hz}$), 8.14 (2H, d, $J=8.8\text{Hz}$)

30 MASS (m/z): 443 (M^++1)

Preparation 56

A solution of 4-(methoxycarbonyl)-O-[4-(7-methoxy-n-heptyloxy)benzoyl]benzamide oxime (6.0 g) in N,N-
35 dimethylformamide (60 ml) was stirred at 100°C for 24 hours.

The reaction mixture was concentrated under reduced pressure and water added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give a solid. The solid was subjected to column chromatography on silica gel (silica gel 60 F254, Merck: 300 g) and eluted with a mixture of ethyl acetate and toluene (1:10-1:5). The fractions containing the objective compound were combined and concentrated under reduced pressure to give methyl 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoate (5.4 g).

IR (KBr): 2939, 2863, 1722, 1612, 1471, 1417, 1270 cm^{-1}

NMR (DMSO- d_6 , δ): 1.15-1.60 (8H, m), 1.60-1.80 (2H, m), 2.10-2.20 (2H, m), 3.21 (3H, s), 3.90 (3H, s), 4.10 (2H, t, $J=6.3\text{Hz}$), 7.20 (2H, d, $J=8.5\text{Hz}$), 8.12-8.27 (6H, m)

MASS (m/z): 425 (M^++1)

Preparation 57

A mixture of methyl 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoate (5.4 g) and 10% sodium hydroxide aqueous solution (15 ml) in ethanol (60 ml) and tetrahydrofuran (30 ml) was stirred at 60-70°C for 2 hours. The reaction mixture was concentrated under reduced pressure and water added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid (4.4 g).

IR (KBr): 2931, 2857, 2667, 2560, 1693, 1614, 1419 cm^{-1}

NMR (DMSO- d_6 , δ): 1.10-1.50 (8H, m), 1.60-1.80 (2H, m), 3.21 (3H, s), 4.10 (2H, t, $J=6.3\text{Hz}$), 7.18 (2H, d, $J=9.1\text{Hz}$), 7.90-8.10 (4H, m), 8.13 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 411 (M^++1)

Preparation 58

To a mixture of 4-[5-[4-(7-methoxy-n-heptyloxy)-phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid (2.0 g) and triethylamine (1.1 g) in dichloromethane (60 ml) was added 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (1.4 g) and 1-hydroxybenzotriazole (0.8 g). The mixture was stirred at room temperature overnight. The reaction mixture was washed with water, brine and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure, and the residue was triturated with isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried to give 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester (2.1 g).

IR (KBr): 2933, 2859, 1781, 1612 cm^{-1}

NMR (CDCl_3 , δ): 1.30-1.70 (8H, m), 1.65-1.90 (2H, m), 3.24 (3H, s), 3.39 (2H, t, $J=6.4\text{Hz}$), 4.06 (2H, t, $J=6.4\text{Hz}$), 7.05 (2H, d, $J=8.9\text{Hz}$), 7.40-7.65 (3H, m), 8.10-8.25 (3H, m), 8.42 (4H, s)

MASS (m/z): 528 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 52.

Preparation 59

Methyl 4-(9-bromo-n-nonyloxy)benzoate

IR (KBr): 2940, 2923, 2856, 1711, 1604, 1511 cm^{-1}

NMR (CDCl_3 , δ): 1.20-1.50 (10H, m), 1.60-1.90 (4H, m), 3.41 (2H, t, $J=6.8\text{Hz}$), 3.88 (3H, s), 4.00 (2H, t, $J=6.8\text{Hz}$), 6.91 (2H, d, $J=8.8\text{Hz}$), 7.98 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 357 (M^+)

The following compound was obtained according to a

similar manner to that of Preparation 53.

Preparation 60

Methyl 4-(9-methoxy-n-nonyloxy)benzoate

5 IR (KBr): 2929, 2852, 1724, 1606 cm^{-1}

NMR (CDCl_3 , δ): 1.20-1.40 (10H, m), 1.45-1.60 (2H, m),
1.65-1.83 (2H, m), 3.33 (3H, s), 3.37 (2H, t,
J=6.5Hz), 3.88 (3H, s), 4.01 (2H, t, J=6.5Hz), 6.90
(2H, d, J=8.9Hz), 8.00 (2H, d, J=8.9Hz)

10 MASS (m/z): 308 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 54.

15 Preparation 61

4-(9-Methoxy-n-nonyloxy)benzoic acid

IR (KBr): 2929, 2856, 2650, 2560, 1695, 1664, 1610 cm^{-1}

NMR (DMSO-d_6 , δ): 1.20-1.35 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.20 (3H, s), 3.28 (2H, t,
20 J=6.4Hz), 4.02 (2H, t, J=6.4Hz), 7.00 (2H, d,
J=8.7Hz), 7.87 (2H, d, J=8.7Hz)

The following compound was obtained according to a similar manner to that of Preparation 55.

25

Preparation 62

4-(Methoxycarbonyl)-O-4'-(9-methoxy-n-nonyloxy)benzoyl-benzamide oxime

IR (KBr): 3488, 3367, 2929, 2856, 1719, 1615, 1589 cm^{-1}

30 NMR (DMSO-d_6 , δ): 1.20-1.40 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.20 (3H, s), 3.28 (2H, t,
J=6.5Hz), 3.89 (3H, s), 4.00 (2H, t, J=6.4Hz), 7.03
(2H, d, J=8.9Hz), 7.07 (2H, br s), 7.92 (2H, d,
J=8.4Hz), 8.05 (2H, d, J=8.4Hz), 8.14 (2H, d,
35 J=8.9Hz)

MASS (m/z): 471 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 56.

5

Preparation 63

Methyl 4-[5-[4-(9-methoxy-n-nonyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoate

IR (KBr): 2933, 2856, 1722, 1616, 1276 cm^{-1}

10 NMR (DMSO- d_6 , δ): 1.20-1.40 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.27-3.33 (2H, m), 3.20 (3H, s),
4.00 (3H, s), 4.05-4.11 (2H, m), 7.19 (2H, d,
J=9Hz), 7.90 (2H, d, J=9Hz), 8.12-8.25 (4H, m)

MASS (m/z): 453 ($M^+ + 1$)

15

The following compound was obtained according to a similar manner to that of Preparation 57.

Preparation 64

20 4-[5-[4-(9-Methoxy-n-nonyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid

IR (KBr): 2931, 2857, 2667, 2560, 1693, 1614, 1419 cm^{-1}

25 NMR (DMSO- d_6 , δ): 1.15-1.40 (10H, m), 1.40-1.50 (2H, m),
1.60-1.80 (2H, m), 3.21 (3H, s), 3.27 (2H, t,
J=6.5Hz), 4.10 (2H, t, J=6.5Hz), 7.18 (2H, d,
J=8.8Hz), 8.10-8.25 (6H, m)

MASS (m/z): 439 ($M^+ + 1$)

30 The following compound was obtained according to a similar manner to that of Preparation 58.

Preparation 65

4-[5-[4-(9-Methoxy-n-nonyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester

35 IR (KBr): 2931, 2856, 1781, 1612 cm^{-1}

NMR (CDCl_3 , δ): 1.20-1.40 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.33 (3H, s), 3.37 (2H, t,
J=6.5Hz), 4.06 (2H, t, J=6.5Hz), 7.05 (2H, d,
J=8.8Hz), 7.40-7.60 (3H, m), 8.10-8.20 (3H, m),
8.42 (4H, br s)
MASS (m/z): 556 ($\text{M}^+ + 1$)

Preparation 66

A mixture of 4-bromophenol (10 g), 1,6-dibromohexane
(49.4 g) and potassium carbonate (9.59 g) in N,N-
dimethylformamide (50 ml) was stirred for 4 hours at 60°C
(bath temp.), and then cooled to ambient temperature. To the
reaction mixture was added ethyl acetate (200 ml), and the
mixture was washed with water (200 ml x 2) and brine. The
organic layer was dried over magnesium sulfate. Magnesium
sulfate was filtered off, and the filtrate was evaporated
under reduced pressure to give a crude product. The crude
product was purified by silica gel chromatography (1:0-1:1
hexane-ethyl acetate) to give 1-bromo-4-(6-bromohexyloxy)-
benzene (15.61 g)

IR (KBr): 2940.9, 2910.1, 2861.8, 1490.7, 1467.6,
1292.1, 1245.8 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.3-1.5 (4H, m), 1.6-2.0 (4H, m), 3.54
(2H, t, J=6.6Hz), 3.94 (2H, t, J=6.4Hz), 6.90 (2H,
d, J=4.5Hz), 7.43 (2H, d, J=4.5Hz)

Preparation 67

A mixture of 1-bromo-4-(6-bromohexyloxy)benzene (6.0 g)
and sodium methylate (28% in methanol) (10.3 ml) in methanol
(30 ml) was stirred for 2 hours at 70°C (bath temp.), and
then the solvent was evaporated. The residue was neutralized
by 1N-hydrochloric acid and extracted with ethyl acetate (100
ml), and washed with water and brine. The organic layer was
dried over magnesium sulfate. Magnesium sulfate was filtered
off, and the filtrate was evaporated under reduced pressure

to give a crude product. The crude product was purified by silica gel chromatography (20:1-10:1 hexane-ethyl acetate) to give 1-bromo-4-(6-methoxyhexyloxy)benzene (15.61 g) as a colorless oil.

5 IR (KBr): 2937.1, 2861.8, 1591.0, 1488.8, 1473.3,
1286.3, 1243.9, 823.5 cm^{-1}
NMR (DMSO- d_6 , δ): 1.2-1.6 (6H, m), 1.6-1.8 (2H, m), 3.21
(3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.93 (2H, t,
10 $J=6.4\text{Hz}$), 6.90 (2H, d, $J=6.8\text{Hz}$), 7.42 (2H, d,
 $J=6.8\text{Hz}$)

Preparation 68

Under a nitrogen atmosphere, to a mixture of 1-bromo-4-(6-methoxyhexyloxy)benzene (3.68 g), 2-methyl-3-butyn-2-ol
15 (1.86 ml) and triethylamine (18 ml) in pyridine (7.4 ml) was added triphenylphosphine (67.2 mg), copper(I) iodide (24.4 mg) and dichlorobis(triphenylphosphine)palladium(II) (18.0 mg), and refluxed overnight. After cooling, insoluble material was filtered off and washed with isopropyl ether.
20 The filtrate was evaporated under reduced pressure. To the residue was added isopropyl ether and the mixture was washed with 0.1N-hydrochloric acid, water and brine. The organic layer was dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under
25 reduced pressure to give a crude yellow oil. The crude yellow oil was purified by silica gel chromatography (10:1-2:1 hexane-ethyl acetate) to give 4-[4-(6-methoxyhexyloxy)-phenyl]-2-methyl-3-butyn-2-ol (3.17 g) as a yellow powder.

IR (KBr): 3426.9, 3415.3, 2979.5, 2937.1, 2858.0,
30 2219.7, 1606.4, 1510.0, 1243.9, 1168.7,
1105.0 cm^{-1}
NMR (DMSO- d_6 , δ): 1.2-1.6 (12H, m), 1.6-1.8 (2H, m),
3.20 (3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.95 (2H, t,
 $J=6.4\text{Hz}$), 5.39 (1H, s), 6.89 (2H, d, $J=8.7\text{Hz}$), 7.29
35 (2H, d, $J=8.7\text{Hz}$)

Preparation 69

Under a nitrogen atmosphere, to a solution of 4-[4-(6-methoxyhexyloxy)phenyl]-2-methyl-3-butyn-2-ol (3.0 g) in
5 toluene (18 ml) was added sodium hydride (abt. 60% in oil suspension), and the mixture was refluxed for 2 hours. After cooling, to the reaction mixture was added isopropyl ether (100 ml) and water (100 ml), and neutralized by 1N-hydrochloric acid. The organic layer was separated, washed
10 with water and brine, dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude red oil. The crude red oil was purified by silica gel chromatography (10:1 hexane-ethyl acetate) to give 1-ethynyl-4-(6-methoxyhexyloxy)benzene (2.39 g) as an orange powder.
15

IR (KBr): 3263.0, 2929.3, 2861.8, 2100.1, 1604.5, 1510.0, 1249.6, 1116.6, 840.8 cm^{-1}

NMR (DMSO- d_6 , δ): 1.2-1.6 (6H, m), 1.6-1.8 (2H, m), 3.21 (3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.97 (2H, t, $J=6.4\text{Hz}$), 4.00 (1H, s), 6.91 (2H, d, $J=8.7\text{Hz}$), 7.39 (2H, d, $J=8.7\text{Hz}$)
20

MASS (m/z): 233.3 ($M^+ + 1$)

Preparation 70

25 To a solution of 4-methoxycarbonylphenylhydroxyimino-methyl chloride (975 mg) and 1-ethynyl-4-(6-methoxyhexyloxy)benzene (1.06 g) in tetrahydrofuran (10 ml) was added triethylamine (0.83 ml) in tetrahydrofuran (10 ml) over a period of 30 minutes at 40°C, and the mixture was
30 stirred at 40°C for 3 hours and 30 minutes. The mixture was diluted with dichloromethane and washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with acetonitrile. The precipitate was collected
35 by filtration and dried to give 4-[5-[4-(6-

methoxyhexyloxy)phenyl]isoxazol-3-yl]benzoic acid methyl ester (1.37 g).

IR (KBr): 2937.1, 2859.9, 1716.3, 1278.6, 1116.6 cm^{-1}

5 NMR (CDCl_3 , δ): 1.3-1.7 (6H, m), 1.7-2.0 (2H, m), 3.34 (3H, s), 3.39 (2H, t, $J=6.3\text{Hz}$), 3.95 (3H, s), 4.02 (2H, t, $J=6.4\text{Hz}$), 4.00 (1H, s), 6.74 (1H, s), 6.98 (2H, d, $J=8.8\text{Hz}$), 7.77 (2H, d, $J=8.8\text{Hz}$), 7.94 (2H, d, $J=8.4\text{Hz}$), 8.14 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 410 (M^++1)

10

Preparation 71

To a solution of 4-[5-[4-(6-methoxyhexyloxy)phenyl]-isoxazol-3-yl]benzoic acid methyl ester (1.0 g) in a mixture of ethanol (10 ml) and tetrahydrofuran (20 ml) was added 10% sodium hydroxide aqueous solution (4.4 ml) and refluxed for 1 hour. The reaction mixture was adjusted to pH 1-2 with 1N-hydrochloric acid, and the resulting precipitate was collected by filtration to give 4-[5-[4-(6-methoxyhexyloxy)phenyl]isoxazol-3-yl]benzoic acid (964.2 mg).

20 IR (KBr): 2939.0, 2863.8, 2669.0, 2545.6, 1685.5, 1616.1, 1284.4, 1253.5 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.2-1.6 (6H, m), 1.6-1.9 (2H, m), 3.21 (3H, s), 3.31 (2H, t, $J=6.2\text{Hz}$), 4.04 (2H, t, $J=6.4\text{Hz}$), 6.11 (2H, d, $J=8.8\text{Hz}$), 7.54 (1H, s), 7.85 (2H, d, $J=8.7\text{Hz}$), 8.07 (2H, d, $J=8.4\text{Hz}$), 8.15 (2H, d, $J=8.4\text{Hz}$)

25

MASS (m/z): 396 (M^++1)

Preparation 72

30 A mixture of 1-bromo-4-fluorobenzene (10 g), cis-2,6-dimethylmorpholine (7.74 ml) and potassium carbonate (15.8 g) in dimethylsulfoxide (50 ml) was stirred for 25 hours at 150°C. The reaction mixture was cooled and poured into water (500 ml), and stirred for 10 minutes. The reaction mixture
35 was extracted with ethyl acetate (100 ml x 2), washed with

brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude yellow oil (680 mg). The crude oil was purified by silica gel chromatography (1:0-10:1 hexane-ethyl acetate) to give 4-(4-bromophenyl)-cis-2,6-dimethylmorpholine (360 mg).

IR (KBr): 2971.8, 2871.5, 1821.3, 1494.6, 1452.1, 1241.9, 1176.4, 1145.5, 1085.7 cm^{-1}

NMR (CDCl_3 , δ): 1.25 (6H, d, $J=6.3\text{Hz}$), 2.39 (2H, t, $J=11.2\text{Hz}$), 3.39 (2H, d, $J=10.4\text{Hz}$), 3.7-3.9 (2H, m), 6.77 (2H, d, $J=9.0\text{Hz}$), 7.34 (2H, d, $J=9.0\text{Hz}$)

MASS (m/z): 270 (M^+)

The following compound was obtained according to a similar manner to that of Preparation 68.

Preparation 73

4-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]-2-methyl-3-butyne-2-ol

IR (KBr): 3326.6, 2979.5, 2931.3, 2873.4, 2832.9, 2223.5, 1606.4, 1511.9, 1454.1, 1376.9, 1334.5, 1238.1, 1174.4, 1151.3, 1081.9 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.14 (6H, d, $J=6.1\text{Hz}$), 1.44 (6H, s), 2.25 (2H, dd, $J=11.0$ and 12.3Hz), 3.5-3.8 (4H, m), 5.34 (1H, s), 6.90 (2H, d, $J=8.9\text{Hz}$), 7.21 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 274 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 69.

Preparation 74

4-(4-Ethynylphenyl)-cis-2,6-dimethylmorpholine

IR (KBr): 3313.1, 2933.2, 2869.6, 2852.2, 2102.0, 1602.6, 1243.9, 1145.5, 1078.0 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.15 (6H, d, $J=6.1\text{Hz}$), 2.27 (2H, t,

$J=11.7\text{Hz}$), 3.6-3.8 (4H, m), 3.93 (1H, s), 6.91 (2H, d, $J=8.9\text{Hz}$), 7.30 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 344 (M^++1)

- 5 The following compound was obtained according to a similar manner to that of Preparation 70.

Preparation 75

10 4-[5-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]isoxazol-3-yl]benzoic acid methyl ester

IR (KBr): 2973.7, 2873.4, 1718.3, 1614.1, 1510.0, 1450.2, 1278.6, 1241.9, 1178.3, 1106.9, 1089.6 cm^{-1}

15 NMR (CDCl_3 , δ): 1.18 (6H, d, $J=6.1\text{Hz}$), 2.36 (2H, t, $J=11.0\text{Hz}$), 3.6-3.9 (4H, m), 3.90 (3H, s), 7.11 (2H, d, $J=8.9\text{Hz}$), 7.48 (1H, s), 7.76 (2H, d, $J=8.8\text{Hz}$), 8.06 (2H, d, $J=8.3\text{Hz}$), 8.11 (2H, d, $J=8.6\text{Hz}$)

MASS (m/z): 393 (M^++1)

- 20 The following compound was obtained according to a similar manner to that of Preparation 71.

Preparation 76

25 4-[5-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]isoxazol-3-yl]benzoic acid

IR (KBr): 3430, 2975, 2857, 2652, 2530, 1689, 1614, 1508, 1450, 1240, 1176 cm^{-1}

30 NMR ($\text{DMSO}-d_6$, δ): 1.18 (6H, d, $J=6.0\text{Hz}$), 2.36 (2H, t, $J=11.1\text{Hz}$), 3.4-4.0 (5H, m), 7.11 (2H, d, $J=8.9\text{Hz}$), 7.46 (1H, s), 7.76 (2H, d, $J=8.7\text{Hz}$), 8.03 (2H, d, $J=8.4\text{Hz}$), 8.09 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 379 (M^++1)

- 35 The following compound was obtained according to a similar manner to that of Preparation 66.

Preparation 77

1-Bromo-4-(8-bromooctyloxy)benzene

IR (KBr): 1937.1, 2856.1, 1490.7, 1471.4, 1290.1,
1247.7, 1014.4 cm^{-1}

NMR (DMSO-d_6 , δ): 1.2-1.6 (8H, m), 1.6-2.0 (4H, m), 3.52
(2H, t, $J=6.7\text{Hz}$), 3.94 (2H, t, $J=6.4\text{Hz}$), 6.89 (2H,
d, $J=8.9\text{Hz}$), 7.42 (2H, d, $J=8.9\text{Hz}$)

The following compound was obtained according to a
similar manner to that of Preparation 67.

Preparation 78

4-[8-(4-Bromophenoxy)octyl]-cis-2,6-dimethylmorpholine

IR (KBr): 2933.2, 2867.6, 2850.3, 1490.7, 1471.4,
1238.1, 1145.5, 1076.1 cm^{-1}

NMR (DMSO-d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (14H,
m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.4\text{Hz}$), 3.4-
3.6 (2H, m), 3.93 (2H, t, $J=6.4\text{Hz}$), 6.89 (2H, d,
 $J=8.9\text{Hz}$), 7.42 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 398 (M^+)

The following compound was obtained according to a
similar manner to that of Preparation 68.

Preparation 79

4-[4-[8-(cis-2,6-Dimethylmorpholin-4-yl)octyloxy]phenyl]-2-methyl-3-butyn-2-ol

IR (KBr): 3187.8, 2973.7, 2933.2, 2858.0, 1602.6,
1506.1, 1469.5, 1241.9, 1164.8, 1139.7,
1081.9 cm^{-1}

NMR (DMSO-d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (20H,
m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.4\text{Hz}$), 3.4-
3.7 (2H, m), 3.95 (2H, t, $J=6.4\text{Hz}$), 5.38 (1H, s),
6.89 (2H, d, $J=8.8\text{Hz}$), 7.29 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 402 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 69.

5

Preparation 80

4-[8-(4-Ethynylphenoxy)octyl]-cis-2,6-dimethylmorpholine

IR (KBr): 3313.1, 2933.2, 2869.6, 2852.2, 2102.0,
1602.6, 1243.9, 1145.5, 1078.0 cm^{-1}

10 NMR (DMSO- d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (14H, m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.4\text{Hz}$), 3.4-3.7 (2H, m), 3.97 (2H, t, $J=6.5\text{Hz}$), 4.00 (1H, s), 6.91 (2H, d, $J=8.7\text{Hz}$), 7.38 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 344 ($M^+ + 1$)

15

The following compound was obtained according to a similar manner to that of Preparation 70.

Preparation 81

20 4-[5-[4-[8-(cis-2,6-Dimethylmorpholin-4-yl)octyloxy]phenyl]isoxazol-3-yl]benzoic acid methyl ester

IR (KBr): 2931.3, 2871.5, 2850.3, 1714.4, 1618.0,
1508.1, 1272.8 cm^{-1}

25 NMR (CDCl_3 , δ): 1.16 (6H, d, $J=6.3\text{Hz}$), 1.2-2.0 (14H, m), 2.2-2.4 (2H, m), 2.75 (2H, d, $J=10.5\text{Hz}$), 3.6-3.8 (2H, m), 3.96 (3H, s), 4.02 (2H, t, $J=6.5\text{Hz}$), 6.74 (1H, s), 6.99 (2H, d, $J=8.8\text{Hz}$), 7.77 (2H, d, $J=8.8\text{Hz}$), 7.94 (2H, d, $J=8.3\text{Hz}$), 8.15 (2H, d, $J=8.3\text{Hz}$)

30 MASS (m/z): 521 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 71.

Preparation 82

4-[5-[4-[8-(cis-2,6-Dimethylmorpholin-4-yl)octyloxy]phenyl]isoxazol-3-yl]benzoic acid

IR (KBr): 3444.2, 2942.8, 2634.3, 2520.5, 1697.1,

5 1618.0 1452.1, 1278.6, 1259.3, 1180.2 cm^{-1}

NMR (CDCl_3 , δ): 1.12 (6H, d, $J=6.3\text{Hz}$), 1.2-1.9 (14H, m),

2.3-2.7 (2H, m), 2.8-3.2 (2H, m), 3.7-4.0 (2H, m),

4.0-4.2 (2H, m), 7.12 (2H, d, $J=8.8\text{Hz}$), 7.56 (1H,

s), 7.86 (2H, d, $J=8.7\text{Hz}$), 8.04 (2H, d, $J=8.5\text{Hz}$),

10 8.10 (2H, d, $J=8.5\text{Hz}$)

MASS (m/z): 493 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 67.

15

Preparation 83

1-Bromo-4-(7-methoxyheptyloxy)benzene

NMR ($\text{DMSO}-d_6$, δ): 1.2-1.6 (8H, m), 1.6-1.8 (2H, m), 3.20

(3H, s), 3.29 (2H, t, $J=6.4\text{Hz}$), 3.96 (2H, t,

20 $J=6.4\text{Hz}$), 5.39 (1H, s), 6.89 (2H, d, $J=8.8\text{Hz}$), 7.29

(2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 301 (M^+)

The following compound was obtained according to a similar manner to that of Preparation 68.

25

Preparation 84

4-[4-(7-Methoxyheptyloxy)phenyl]-2-methyl-3-butyn-2-ol

IR (KBr): 3394.1, 3309.2, 2979.5, 2939.0, 2871.5,

30 2852.2, 1606.4, 1510.0, 1469.5, 1247.7,

1160.9 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.2-1.6 (14H, m), 1.6-1.8 (2H, m),

3.20 (3H, s), 3.29 (2H, t, $J=6.4\text{Hz}$), 3.93 (2H, t,

$J=6.5\text{Hz}$), 6.89 (2H, d, $J=9.0\text{Hz}$), 7.42 (2H, d,

35 $J=9.0\text{Hz}$)

MASS (m/z): 305.2 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 69.

5

Preparation 85

1-Ethynyl-4-(7-methoxyheptyloxy)benzene

IR (KBr): 3313.1, 3290.0, 2935.1, 2859.9, 2105.9,
1606.4, 1506.1, 1247.7, 1114.7 cm^{-1}

10 NMR ($\text{DMSO}-d_6$, δ): 1.2-1.6 (8H, m), 1.6-1.8 (2H, m), 3.20
(3H, s), 3.29 (2H, t, $J=6.4\text{Hz}$), 3.97 (2H, t,
 $J=6.5\text{Hz}$), 6.92 (2H, d, $J=8.9\text{Hz}$), 7.39 (2H, d,
 $J=8.8\text{Hz}$)

MASS (m/z): 247.2 ($M^+ + 1$)

15

The following compound was obtained according to a similar manner to that of Preparation 70.

Preparation 86

20 4-[5-[4-(7-Methoxyheptyloxy)phenyl]isoxazol-3-yl]benzoic
acid methyl ester

IR (KBr): 2935.1, 2861.8, 1720.2, 1618.0, 1436.7,
1276.6, 1112.7 cm^{-1}

25 NMR (CDCl_3 , δ): 1.2-1.7 (8H, m), 1.7-2.0 (2H, m), 3.34
(3H, s), 3.38 (2H, t, $J=6.5\text{Hz}$), 3.96 (3H, s), 4.02
(2H, t, $J=6.4\text{Hz}$), 6.75 (1H, s), 6.99 (2H, d,
 $J=8.9\text{Hz}$), 7.77 (2H, d, $J=8.8\text{Hz}$), 7.94 (2H, d,
 $J=8.5\text{Hz}$), 8.15 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 424 ($M^+ + 1$)

30

The following compound was obtained according to a similar manner to that of Preparation 71.

Preparation 87

35 4-[5-[4-(7-Methoxyheptyloxy)phenyl]isoxazol-3-yl]benzoic

acid

IR (KBr): 2933.2, 2856.1, 2669.0, 2549.1, 1683.6,
1614.1, 1506.1, 1454.1, 1427.1, 1284.4, 1257.4,
1120.4 cm^{-1}

5 NMR (DMSO-d_6 , δ): 1.2-1.6 (8H, m), 1.7-1.9 (2H, m), 3.21
(3H, s), 3.2-3.5 (2H, m), 4.0-4.2 (2H, m), 7.0-7.2
(2H, m), 7.5 (1H, s), 7.8-8.0 (2H, m), 8.0-8.2 (4H,
m)

MASS (m/z): 410 ($M^+ + 1$)

10

The following compound was obtained according to a
similar manner to that of Preparation 66.

Preparation 88

15 1-Bromo-4-(7-bromoheptyloxy)benzene

IR (KBr): 2939.0, 2910.1, 2856.1, 1591.0, 1488.8,
1467.6, 1288.2, 1245.8 cm^{-1}

NMR (DMSO-d_6 , δ): 1.2-1.5 (6H, m), 1.6-1.9 (4H, m), 3.53
(2H, t, $J=6.7\text{Hz}$), 3.94 (2H, t, $J=6.5\text{Hz}$), 6.90 (2H,
20 d, $J=9.0\text{Hz}$), 7.42 (2H, d, $J=9.0\text{Hz}$)

MASS (m/z): 350 (M^+)

Preparation 89

A mixture of 1-bromo-4-(7-bromoheptyloxy)benzene (4.405
25 g), cis-2,6-dimethylmorpholine (1.55 ml) and potassium
carbonate (2.09 g) in N,N-dimethylformamide (22 ml) was
stirred for 1 hour at 70°C. To the reaction mixture was
added cis-2,6-dimethylmorpholine (7.75 ml) and stirred for 1
hour at 70°C. Ethyl acetate (100 ml) was added, and the
30 mixture washed with water (50 ml x 2) and brine. The
separated organic layer was dried over magnesium sulfate and
evaporated under reduced pressure to give a crude pale yellow
oil (5.30 g). The crude oil was purified by silica gel
chromatography (20:1-1:2 hexane-ethyl acetate) to give 4-[7-
35 (4-bromophenoxy)heptyl]-cis-2,6-dimethylmorpholine (4.43 g)

as a pale yellow oil.

IR (KBr): 2971.8, 2935.1, 2859.9, 2811.7, 2773.1,
1488.8, 1469.5, 1243.9, 1145.5, 1078 cm^{-1}

5 NMR (DMSO- d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (12H, m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.5\text{Hz}$), 3.4-3.6 (2H, m), 3.94 (2H, t, $J=6.4\text{Hz}$), 6.89 (2H, d, $J=8.9\text{Hz}$), 7.42 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 386 (M^++2)

10 The following compound was obtained according to a similar manner to that of Preparation 68.

Preparation 90

15 4-[4-[7-(cis-2,6-Dimethylmorpholin-4-yl)heptyloxy]-phenyl]-2-methyl-3-butyn-2-ol

IR (KBr): 3151.1, 2973.7, 2935.1, 2859.9, 2825.2,
1604.5, 1506.1, 1243.9, 1160.9, 1139.7 cm^{-1}

20 NMR (DMSO- d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (18H, m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.2\text{Hz}$), 3.4-3.7 (2H, m), 3.95 (2H, t, $J=6.4\text{Hz}$), 5.39 (1H, s), 6.89 (2H, d, $J=8.7\text{Hz}$), 7.28 (2H, d, $J=8.6\text{Hz}$)

MASS (m/z): 388 (M^++1)

25 The following compound was obtained according to a similar manner to that of Preparation 69.

Preparation 91

30 4-[7-(4-Ethynylphenoxy)heptyl]-cis-2,6-dimethylmorpholine

IR (KBr): 3290.0, 2971.8, 2935.1, 2859.9, 2811.7,
2775.1, 2105.9, 1606.4, 1506.1, 1469.5, 1288.2,
1247.7, 1170.6, 1145.5, 1079.9, 833.1 cm^{-1}

35 NMR (DMSO- d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (12H, m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.3\text{Hz}$), 3.4-3.6 (2H, m), 3.95 (2H, t, $J=6.5\text{Hz}$), 4.00 (1H, s),

6.92 (2H, d, J=8.8Hz), 7.39 (2H, d, J=8.7Hz)
MASS (m/z): 330 ($M^+ + 1$)

The following compound was obtained according to a
5 similar manner to that of Preparation 70.

Preparation 92

4-[5-[4-[7-(cis-2,6-Dimethylmorpholin-4-yl)heptyloxy]phenyl]isoxazol-3-yl]benzoic acid methyl ester.

10 IR (KBr): 2946.7, 2931.3, 2869.6, 2815.6, 2767.3,
1720.2, 1616.1, 1506.1, 1450.2, 1434.8, 1307.5,
1270.9, 1178.3, 1143.6, 1105.0 1078.0 cm^{-1}
NMR (CDCl_3 , δ): 1.16 (6H, d, J=6.3Hz), 1.2-2.0 (12H, m),
2.2-2.4 (2H, m), 2.75 (2H, d, J=10.4Hz), 3.5-3.9
15 (2H, m), 3.96 (3H, s), 4.02 (2H, t, J=6.5Hz), 6.75
(1H, s), 6.99 (2H, d, J=8.8Hz), 7.77 (2H, d,
J=8.8Hz), 7.94 (2H, d, J=8.5Hz), 8.15 (2H, d,
J=8.4Hz)
MASS (m/z): 507 ($M^+ + 1$)

20

The following compound was obtained according to a
similar manner to that of Preparation 71.

Preparation 93

25 4-[5-[4-[7-(cis-2,6-Dimethylmorpholin-4-yl)heptyloxy]-
phenyl]isoxazol-3-yl]benzoic acid

IR (KBr): 3446.2, 2939.0, 2636.2, 2520.5, 1693.2,
1618.0, 1508.1, 1452.1, 1265.1 cm^{-1}
NMR (DMSO-d_6 , δ): 1.12 (6H, d, J=6.2Hz), 1.2-1.9 (12H,
30 m), 2.3-2.7 (2H, m), 2.8-3.2 (2H, m), 3.7-4.0 (2H,
m), 4.07 (2H, t, J=6.3Hz), 7.13 (2H, d, J=8.8Hz),
7.55 (1H, s), 7.86 (2H, d, J=8.5Hz), 8.04 (2H, d,
J=8.5Hz), 8.10 (2H, d, J=8.4Hz)
MASS (m/z): 507 ($M^+ + 1$)

35

Preparation 94

To a solution of 4-hydroxypiperidine (15 g) in a mixture of tetrahydrofuran (THF) (150 ml) and water (100 ml) was added dropwise a solution of di-tert-butyl dicarbonate (48.5 g) in THF (100 ml) keeping pH 9 with 1N-sodium hydroxide under ice-cooling. The mixture was stirred at ambient temperature for 1 hour. The reaction mixture was successively washed with water and saturated sodium chloride, dried over anhydrous magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give crystals. The crystals were washed with n-hexane (300 ml), collected by filtration and dried in vacuo to give 1-N-t-butyloxycarbonyl-4-hydroxypiperidine (24.66 g).

Preparation 95

To a solution of 1-N-t-butyloxycarbonyl-4-hydroxypiperidine (5.0 g) in dimethylformamide (DMF) (25 ml) was portionwise added sodium hydride (60% in oil) (1.29 g) with stirring under ice-cooling. The mixture was successively stirred at ambient temperature for 30 minutes, stirred at 60°C for 1 hour and cooled with an ice bath. To the reaction mixture was added 1,5-dibromopentane (6.72 ml), and the mixture was stirred at ambient temperature for 3 hours. The reaction solution was poured into water (100 ml) and extracted twice with a mixture of ethyl acetate (80 ml) and n-hexane (30 ml). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-bromopentyloxy)-1-N-t-butyloxycarbonylpiperidine (2.44 g).

NMR (CDCl₃, δ): 1.46 (9H, s), 1.50-1.70 (6H, m), 1.70-

1.96 (4H, m), 3.00-3.15 (2H, m), 3.35-3.50 (5H, m),
3.70-3.90 (2H, m)

APCI MASS (m/z): 250 (M^+ -101)

5 Preparation 96

To a solution of 4-(5-bromopentyloxy)-1-N-t-butylloxycarbonylpiperidine (2.44 g) in methanol (13 ml) was added 28% sodium methoxide methanol solution (14.2 ml), and the mixture was stirred under reflux for 4 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (250 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-1-N-t-butylloxycarbonylpiperidine (1.97 g).

NMR ($CDCl_3$, δ): 1.45 (9H, s), 1.45-1.95 (10H, m), 3.03 (1H, dd, $J=3.47$ and 9.20Hz), 3.10 (1H, dd, $J=3.47$ and 9.20Hz), 3.44 (3H, s), 3.34-3.50 (5H, m), 3.70-3.85 (2H, m)

APCI MASS (m/z): 202 (M^+ -101)

Preparation 97

To a solution of 4-(5-methoxypentyloxy)-1-N-t-butylloxycarbonylpiperidine (1.97 g) in ethyl acetate (20 ml) was added 4N-hydrogen chloride ethyl acetate solution (16.3 ml), and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in a mixture of dichloromethane and methanol (10:1; 50 ml:5 ml). To this solution was added 1N-sodium hydroxide (5 ml) with stirring. The organic layer was separated and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)piperidine (0.62 g).

NMR ($CDCl_3$, δ): 1.25-1.50 (2H, s), 1.50-1.75 (6H, m), 1.90-2.10 (2H, m), 2.70-2.90 (2H, m), 2.95-3.20 (2H, m), 3.33 (3H, s), 3.35-3.50 (5H, m)

APCI MASS (m/z): 202 (M^+)

Preparation 98

A solution of 4-fluorobenzonitrile (0.38 g), 4-(5-methoxypentyloxy)piperidine (0.62 g) and potassium carbonate (0.87 g) in DMF (8 ml) was stirred at 90-95°C for 6 hours. The reaction mixture was poured into water (50 ml) and extracted twice with a mixture of ethyl acetate and n-hexane (50 ml:20 ml). The extracts were combined, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v - 2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-N-(4-cyanophenyl)piperidine (294 mg).

NMR ($CDCl_3$, δ): 1.35-1.55 (2H, s), 1.55-1.75 (5H, m), 1.85-2.05 (2H, m), 3.13 (1H, dd, $J=3.47$ and 9.20Hz), 3.17 (1H, dd, $J=3.47$ and 9.20Hz), 3.33 (3H, s), 3.35-3.75 (8H, m), 6.85 (2H, d, $J=9.01$ Hz), 7.47 (2H, d, $J=8.96$ Hz)

APCI MASS (m/z): 303 (M^+)

Preparation 99

A solution of 4-(5-methoxypentyloxy)-N-(4-cyanophenyl)piperidine (294 mg) and thiosemicarbazide (0.68 g) in toluene (20 ml) and trifluoroacetic acid (10 ml) was stirred at 60-65°C for 7 hours. After cooling, the reaction mixture was poured into a mixture of water (100 ml) and ethyl acetate (200 ml) and adjusted to pH 10 with 1N-sodium hydroxide. The mixture was dissolved in a mixture of THF (50 ml) and methanol (10 ml). The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitate was washed with isopropyl ether and

dried in vacuo to give 2-amino-5-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.29 g).

5 NMR (CDCl₃+CD₃OD, δ): 1.30-1.50 (2H, m), 1.50-1.80 (6H, m), 1.90-2.10 (2H, m), 2.90-3.10 (2H, m), 3.34 (3H, s), 3.35-3.70 (7H, m), 6.93 (2H, d, J=8.91Hz), 7.63 (2H, d, J=8.83Hz)

APCI MASS (m/z): 377 (M⁺)

10 Preparation 100

To a suspension of 2-amino-5-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.29 g) in ethanol (20 ml) was added ethyl 4-bromoacetylbenzoate (1.39 g) and stirred at reflux for 5
15 hours. The reaction mixture was cooled and poured into diisopropyl ether (IPE) (60 ml). The resulting precipitate was collected by filtration and dried. To a suspension of the precipitate in xylene (40 ml) was added trifluoroacetic acid (4 ml), and the mixture was stirred at reflux (130°C)
20 for 5 hours. The reaction mixture was cooled and poured into IPE (300 ml). The resulting precipitate was filtered and dried to give 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g).

25 NMR (CDCl₃, δ): 1.42 (3H, t, J=7.12Hz), 1.45-1.75 (6H, m), 1.85-2.10 (2H, m), 2.30-2.50 (2H, m), 3.36 (3H, s), 3.35-3.55 (5H, m), 3.60-3.80 (2H, m), 4.40 (2H, q, J=7.14Hz), 7.57 (2H, d, J=8.78Hz), 7.84 (2H, d, J=8.40Hz), 7.91 (2H, d, J=8.79Hz), 8.13 (1H, s)

30 ESI MASS (m/z): 549 (M⁺+1)

Preparation 101

To a solution of 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g)
35

in a mixture of methanol (40 ml) and tetrahydrofuran (20 ml) was added 4N-NaOH (20 ml), and the mixture was refluxed for 6 hours. The reaction mixture was cooled, poured into water (200 ml) and adjusted to pH 2 with conc. HCl. The resulting
5 precipitate was collected by filtration, washed in turn with water, isopropyl alcohol (30 ml) and IPE (50 ml) to give 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g).

10 ESI MASS (m/z)(Negative): 519.2 ($M^+ + 1$)

Preparation 102

To a solution of 4-[2-[4-[4-(5-methoxypentyloxy)-piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g) and 1-hydroxybenzotriazole (465 mg)
15 in dichloromethane (50 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (943 mg), and the mixture was stirred overnight at ambient temperature. The reaction mixture was evaporated in vacuo.
20 To the resulting precipitate was added water (50 ml), and the solid was washed with water and IPE (50 ml) and dried under reduced pressure for 3 hours to give 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
25 benzotriazol-1-yl ester (1.26 g).

IR (KBr): 1774.2, 1708.6, 1604.5, 1471.4 1365.4, 1230.4 cm^{-1}

NMR (CDCl_3 , δ): 1.30-1.80 (8H, m), 1.85-2.10 (2H, m),
3.05-3.30 (2H, m), 3.33 (3H, s), 3.35-3.55 (4H, m),
30 3.55-3.75 (2H, m), 6.94 (2H, d, $J=8.94\text{Hz}$), 7.30-7.60 (3H, m), 7.73 (2H, d, $J=8.79\text{Hz}$), 8.00-8.20 (4H, m), 8.30 (2H, d, $J=8.46\text{Hz}$)

ESI MASS (m/z)(Positive): 660.1 ($M^+ + \text{Na}$)

Preparation 103

To a solution of 4-hydroxy-N-(benzyloxycarbonyl)-piperidine (5.0 g) in THF (50 ml) were added 3-bromocyclohexene (3.67 ml) and silver oxide (7.4 g). The mixture was stirred at ambient temperature overnight. To the solution were added 3-bromocyclohexene (4.0 ml) and silver oxide (5.0 g), and the mixture was stirred at 40°C for 6 hours. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The resulting residue was chromatographed on silica gel (300 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(2-cyclohexenyloxy)-N-(benzyloxycarbonyl)piperidine (3.83 g).

NMR (CDCl₃, δ): 1.40-2.20 (12H, m), 3.10-3.30 (2H, m), 3.50-3.70 (1H, m), 3.80-4.10 (3H, m), 5.12 (2H, s), 5.40-5.90 (2H, m), 7.35 (5H, m)

ESI MASS (m/z)(Positive): 338.3 (M⁺+Na)

Preparation 104

A solution of 4-(2-cyclohexenyloxy)-N-(benzyloxycarbonyl)piperidine (3.80 g), and 10% palladium on carbon (50% wet) (1.0 g) in methanol (40 ml) was hydrogenated under an atmospheric pressure of hydrogen at ambient temperature for 6 hours. The catalyst was filtered off, and the filtrate was evaporated in vacuo and dried in vacuo to give 4-(cyclohexyloxy)piperidine (2.42 g).

NMR (CDCl₃, δ): 1.10-1.40 (4H, m), 1.40-2.00 (10H, m), 2.60-2.90 (2H, m), 3.05-3.20 (2H, m), 3.30-3.50 (1H, m), 3.50-3.75 (1H, m)

APCI MASS (m/z): 184.4 (M⁺+1)

Preparation 105

A solution of 4-fluorobenzonitrile (1.50 g), 4-(cyclohexyloxy)piperidine (2.40 g) and potassium carbonate

(3.3 g) in DMF (30 ml) was stirred at 90-95°C for 6 hours. The reaction mixture was poured into water (100 ml) and extracted twice with a mixture of ethyl acetate and n-hexane (80 ml:30 ml). The extracts were combined, washed with
5 saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (6:1 v/v-5:1 v/v). The
10 fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-[4-cyclohexyloxypiperidin-1-yl]benzonitrile (1.90 g).

NMR (CDCl₃, δ): 1.10-1.40 (5H, m), 1.40-2.00 (9H, m),
3.00-3.20 (2H, m), 3.20-3.45 (1H, m), 3.55-3.80
(3H, m), 6.85 (2H, d, J=8.99Hz), 7.46 (2H, d,
15 J=8.95Hz)

APCI MASS (m/z): 285 (M⁺)

Preparation 106

A solution of 4-(4-cyclohexyloxypiperidin-1-yl)benzonitrile (1.90 g), thiosemicarbazide (0.91 g) in
20 toluene (20 ml) and trifluoroacetic acid (10 ml) was stirred at 60-65°C with stirring for 7 hours. After cooling, the reaction mixture was poured into a mixture of water (100 ml) and ethyl acetate (100 ml) and adjusted to pH 10 with 1N-
25 sodium hydroxide. The mixture was dissolved in a mixture of THF (50 ml) and ethyl acetate (100 ml). The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in
vacuo. The resulting precipitate was washed diisopropyl
30 ether and dried in vacuo to give 2-amino-5-[4-[4-(cyclohexyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.72 g).

NMR (DMSO-d₆, δ): 1.10-1.45 (4H, m), 1.45-1.95 (10H, m),
2.85-3.10 (2H, m), 3.25-3.45 (1H, m), 3.50-3.80
35 (3H, m), 6.97 (2H, d, J=8.92Hz), 7.54 (2H, d,

J=8.80Hz)

APCI MASS (m/z): 360 ($M^+ + 1$)

Preparation 107

5 To a suspension of 2-amino-5-[4-[4-(cyclohexyloxy)-
piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.72 g) in ethanol
(30 ml) was added ethyl 4-bromoacetylbenzoate (1.95 g) and
the mixture was stirred at reflux for 5 hours. The reaction
mixture was cooled and poured into IPE (60 ml). The
10 resulting precipitate was collected by filtration and dried.
To a suspension of the precipitate in xylene (40 ml) was
added trifluoroacetic acid (4 ml), and the mixture was
stirred at reflux (130°C) for 5 hours. The reaction mixture
was cooled and poured into IPE (300 ml). The resulting
15 precipitate was filtered and dried to give 4-[2-[4-[4-
(cyclohexyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]-
thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid
salt (2.01 g). This compound was immediately used as the
starting compound for the next step.

20

The following compound was obtained according to a
similar manner to that of Preparation 101.

Preparation 108

25 4-[2-[4-[4-(Cyclohexyloxy)piperidin-1-
yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
NMR ($CDCl_3 + CD_3OD$, δ): 1.10-2.10 (14H, m), 2.90-3.20 (2H,
m), 4.20-4.60 (1H, m), 6.96 (2H, d, J=8.24Hz),
7.50-8.20 (7H, m)
30 ESI MASS (m/z): 525.3 ($M^+ + Na$)

The following compound was obtained according to a
similar manner to that of Preparation 102.

Preparation 109

4-[2-[4-[4-(Cyclohexyloxy)piperidin-1-yl]phenyl]-
imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
benzotriazol-1-yl ester

5 IR (KBr): 1772, 1703, 1606, 1470, 1369 cm^{-1}

Preparation 110

To a solution of 4-(4-methanesulfonyloxypiperidin-1-
yl)benzonitrile (4.90 g) in N,N-dimethylformamide (DMF) (50
10 ml) were added potassium carbonate (4.83 g) and 2,6-
dimethylmorpholine (3.02 g), and the mixture was stirred at
90-95°C for 6 hours. After cooling, the reaction mixture was
poured into water (300 ml) and extracted twice with a mixture
of ethyl acetate and n-hexane (100 ml:30 ml). The extracts
15 were combined and washed in turn with water and saturated
aqueous sodium chloride, dried over anhydrous magnesium
sulfate and evaporated in vacuo. The resulting precipitates
were washed with IPE (100 ml), collected by filtration and
dried in vacuo to give 4-[4-(2,6-dimethylmorpholin-4-
20 yl)piperidin-1-yl]benzonitrile (2.29 g).

NMR (CDCl_3 , δ): 1.18 (6H, d, $J=6.03\text{Hz}$), 1.60-1.90 (2H,
m), 1.90-2.15 (2H, m), 2.35-2.60 (2H, m), 3.10-3.30
(2H, m), 3.40-4.10 (6H, m), 4.80-5.05 (1H, m), 6.87
(2H, d, $J=8.97\text{Hz}$), 7.48 (2H, d, $J=8.96\text{Hz}$)

25 APCI MASS (m/z): 300 (M^+)

The following compound was obtained according to a
similar manner to that of Preparation 99.

Preparation 111

2-Amino-5-[4-[4-(2,6-dimethylmorpholin-4-yl)piperidin-1-
yl]phenyl]-1,3,4-thiadiazole

NMR (CDCl_3 , δ): 1.19 (6H, d, $J=6.22\text{Hz}$), 1.70-2.15 (4H,
m), 3.10-3.25 (2H, m), 3.40-3.70 (4H, m), 3.70-4.10
35 (2H, m), 4.80-5.00 (1H, m), 6.94 (2H, d, $J=8.88\text{Hz}$),

7.65 (2H, d, J=8.82Hz)

APCI MASS (m/z): 374 (M^+)

The following compound was obtained according to a
5 similar manner to that of Preparation 100.

Preparation 112

4-[2-[4-[4-(2,6-Dimethylmorpholin-4-yl)piperidin-1-
yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
10 ethyl ester trifluoroacetic acid salt.

NMR ($CDCl_3$, δ): 1.19 (6H, d, J=6.20Hz), 1.41 (3H, t,
J=7.11Hz), 1.70-1.90 (2H, m), 1.90-2.20 (2H, m),
2.40-2.65 (2H, m), 3.20-3.40 (2H, m), 3.40-4.30
(8H, m), 4.39 (2H, q, J=7.07Hz), 4.85-5.10 (1H, m),
15 7.02 (2H, d, J=8.93Hz), 7.76 (2H, d, J=8.81Hz),
7.87 (2H, d, J=8.34Hz), 8.08 (1H, s), 8.11 (2H, d,
J=9.71Hz)

The following compound was obtained according to a
20 similar manner to that of Preparation 101.

Preparation 113

4-[2-[4-[4-(2,6-Dimethylmorpholin-4-yl)piperidin-1-
yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
25 APCI MASS (m/z): 519 (M^++1)

The following compound was obtained according to a
similar manner to that of Preparation 102.

30 Preparation 114

4-[2-[4-[4-(2,6-Dimethylmorpholin-4-yl)piperidin-1-
yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1774, 1691, 1605, 1466, 1429, 1232 cm^{-1}

Preparation 115

A solution of 4-[4-(methanesulfonyloxy)piperidin-1-yl]nitrobenzene (2.0 g), and potassium thioacetate (1.14 g) in dimethylsulfoxide (DMSO) (20 ml) was stirred at 100-110°C for 3 hours. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (100 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitates were washed with IPE (50 ml), collected by filtration and dried in vacuo to give 4-(4-acetylthiopiperidin-1-yl)nitrobenzene (1.15 g).

NMR (CDCl₃, δ): 1.60-1.85 (2H, m), 2.00-2.20 (2H, m), 2.34 (3H, s), 3.15-3.35 (2H, m), 3.65-3.90 (3H, m), 6.81 (2H, d, J=9.47Hz), 8.12 (2H, d, J=9.43Hz)

APCI MASS (m/z): 281 (M⁺)

Preparation 116

To a solution of 4-(4-acetylthiopiperidin-1-yl)nitrobenzene (3.34 g) in a mixture of THF (30 ml) and methanol (30 ml) was added 28% sodium methoxide methanol solution (2.67 ml) at 0-5°C and stirred at the same temperature for 30 minutes. To the mixture was added iodopropane (1.51 ml) at the same temperature and stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo and dissolved in ethyl acetate (100 ml). The solution was washed three times with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. A solution of the resulting residue, ammonium chloride (1.0 g) and iron powder (4.0 g) in a mixture of ethanol (60 ml) and water (30 ml) was refluxed for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (300 ml) eluting with ethyl acetate. The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(4-propylthiopiperidin-1-yl)aniline (2.47

g).

NMR (CDCl_3 , δ): 1.00 (3H, t, $J=7.16\text{Hz}$), 1.50-1.90 (4H, m), 1.95-2.15 (2H, m), 2.55 (2H, t, $J=7.56\text{Hz}$), 2.60-2.80 (3H, m), 3.35-3.55 (4H, m), 6.63 (2H, d, $J=8.81\text{Hz}$), 6.81 (2H, d, $J=8.80\text{Hz}$)

APCI MASS (m/z): 251 (M^+)

Preparation 117

A solution of 4-(4-propylthiopiperidin-1-yl)aniline (2.44 g), 1-[2-(p-toluenesulfonyloxy)ethyl]-2-oxazolidone (3.08 g) and potassium carbonate (3.28 g) in a mixture of acetonitrile (25 ml) and DMF (13 ml) was stirred at 120°C for 5 hours. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (60 ml). The extracts were collected, washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with ethyl acetate. The fractions containing the desired compound were collected and evaporated under reduced pressure to give 1-[(2-oxazolidon-3-yl)ethylamino]-4-[4-(propylthio)piperidin-1-yl]benzene (1.98 g).

NMR (CDCl_3 , δ): 1.00 (3H, t, $J=7.34\text{Hz}$), 1.50-1.90 (5H, m), 2.00-2.20 (2H, m), 2.55 (2H, t, $J=7.5\text{Hz}$), 2.55-2.90 (3H, m), 3.10-3.65 (8H, m), 4.29 (2H, dd, $J=6.56$ and 8.29Hz), 6.40-6.70 (2H, m), 6.70-6.95 (2H, m)

APCI MASS (m/z): 364 (M^+)

Preparation 118

A solution of 1-[(2-oxazolidon-3-yl)ethylamino]-4-(4-propylthiopiperidin-1-yl)benzene (1.96 g) in 30% HBr in acetic acid solution (15 ml) was stirred at ambient temperature overnight. IPE (100 ml) was added to the reaction mixture, and the resulting precipitates were

collected by filtration, washed with IPE (40 ml) and dried under reduced pressure. The precipitates were dissolved in a mixture of ethanol (20 ml) and n-butylalcohol (40 ml), and the solution was refluxed for 6 hours. After cooling, to the reaction mixture was added IPE (100 ml), and the resulting precipitates were collected by filtration, washed with IPE (20 ml) and dried in vacuo to give 1-[4-(4-propylthiopiperidin-1-yl)phenyl-1-yl]piperazine (2.51 g).

10 NMR (CDCl₃+CD₃OD, δ): 1.03 (3H, t, J=6.98Hz), 1.50-1.90 (2H, m), 2.10-2.40 (3H, m), 2.50-2.90 (5H, m), 6.80-7.00 (2H, m), 7.55-7.70 (2H, m)

APCI MASS (m/z): 320 (M⁺)

Preparation 119

15 A solution of 1-[4-(4-propylthiopiperidin-1-yl)benzen-1-yl]piperazine (2.45 g) and potassium carbonate (2.81 g) in N,N-dimethylsulfoxide (30 ml) was stirred at 100°C for 30 minutes and then at 150°C for 5 hours. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (100 ml). The extracts were collected, washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of dichloromethane and methanol (9:1 v/v).
20 The fractions containing the desired compound were collected and evaporated under reduced pressure and washed with IPE. The precipitates were collected by filtration and dried in vacuo to give 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid ethyl ester (1.22 g).

30 NMR (CDCl₃, δ): 1.01 (3H, t, J=7.36Hz), 1.37 (3H, t, J=7.79Hz), 1.50-1.90 (4H, m), 2.00-2.20 (2H, m), 2.56 (2H, t, J=7.53Hz), 2.65-2.90 (3H, m), 3.15-3.30 (4H, m), 3.40-3.60 (6H, m), 4.33 (2H, q, J=7.11Hz), 6.91 (2H, d, J=9.10Hz), 6.92 (4H, s), 7.95 (2H, d, J=8.97Hz)
35

APCI MASS (m/z): 468 (M^+)

Preparation 120

To a solution of 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid ethyl ester (1.22 g) in a mixture of ethanol (10 ml) and tetrahydrofuran (40 ml) was added 10% aqueous NaOH (2.1 ml) and 1N-NaOH (10 ml), and the mixture was refluxed for 6 hours. The reaction mixture was cooled and adjusted to pH 2.5-3.0 with 1N-HCl. The resulting precipitates were collected by filtration, washed in turn with water (30 ml) and IPE (50 ml) and dried in vacuo to give 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid (0.99 g).

NMR (DMSO- d_6 , δ): 0.94 (3H, t, $J=7.38\text{Hz}$), 1.40-1.70 (5H, m), 1.85-2.15 (2H, m), 2.60-2.90 (4H, m), 3.00-3.20 (5H, m), 3.30-3.55 (6H, m), 6.88 (4H, s), 7.01 (2H, d, $J=9.00\text{Hz}$), 7.78 (2H, d, $J=8.89\text{Hz}$)

APCI MASS (m/z): 440 (M^+)

Preparation 121

To a solution of 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid (0.98 g), 1-hydroxybenzotriazole (0.39 g) in dichloromethane (20 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (0.85 g), and the mixture was stirred for 15 minutes. To the solution was added triethylamine (0.31 ml), and the mixture was stirred overnight at ambient temperature. The reaction mixture was poured into a mixture of 0.1N-hydrochloric acid (25 ml) and dichloromethane (60 ml). The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. To the resulting precipitates were washed with water and IPE (50 ml), collected by filtration and dried under reduced pressure to give 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-

4-yl]benzoic acid benzotriazol-1-yl ester (1.04 g).

NMR (CDCl₃, δ): 1.01 (3H, t, J=7.36Hz), 1.50-1.90 (5H, m), 2.00-2.20 (2H, m), 2.56 (2H, t, J=7.56Hz), 2.65-2.90 (3H, m), 3.20-3.30 (4H, m), 3.45-3.70 (6H, m), 6.94 (4H, s), 7.00 (2H, d, J=9.19Hz), 7.35-7.60 (3H, m), 8.05-8.20 (3H, m)

APCI MASS (m/z): 557 (M⁺)

Preparation 122

To a solution of N-t-butyloxycarbonyl-4-acetylthiopiperidine (5.5 g) in a mixture of THF (50 ml) and methanol (50 ml) was added 28% sodium methoxide methanol solution (4.76 ml) with stirring under ice-cooling and stirred at the same temperature for 30 minutes. To the solution was added 1,6-dibromohexane (17.1 g) under ice-cooling, and the mixture was successively stirred at ambient temperature for 30 minutes and then stirred at 45°C for 2 hours. The reaction mixture was concentrated in vacuo. The resulting residue was chromatographed on silica gel (500 ml) eluting with a mixture of n-hexane and ethyl acetate (6:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(6-bromohexylthio)-N-t-butyloxycarbonylpiperidine (4.95 g).

NMR (CDCl₃, δ): 1.45 (9H, s), 1.45-1.70 (8H, m), 1.80-2.00 (4H, m), 2.55 (1H, t, J=7.34Hz), 2.65-3.05 (3H, m), 3.30-3.50 (2H, m), 3.85-4.10 (2H, m)

APCI MASS (m/z): 250 (M⁺-101)

Preparation 123

To a solution of 4-(6-bromohexylthio)-N-t-butyloxycarbonylpiperidine (4.95 g) in methanol (20 ml) was added 28% sodium methoxide methanol solution (26.6 ml), and the mixture was stirred under reflux for 4 hours. After cooling, the reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml)

eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(6-methoxyhexylthio)-N-t-butyloxycarbonylpiperidine (3.32 g).

5 NMR (CDCl₃, δ): 1.25-1.45 (6H, m), 1.45 (9H, s), 1.45-1.60 (4H, m), 1.80-2.00 (2H, m), 2.54 (2H, t, J=7.47Hz), 2.60-3.00 (3H, m), 3.30 (3H, s), 3.37 (2H, t, J=6.34Hz), 3.96 (2H, m)

10 Preparation 124

To a solution of 4-(6-methoxyhexylthio)-N-t-butoxycarbonylpiperidine (3.32 g) in dichloromethane (40 ml) were added triethylsilane (8.0 ml) and trifluoroacetic acid (15.4 ml) with stirring in an ice bath. The mixture was
15 stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml) eluting with a mixture of dichloromethane and methanol (4:1 v/v). The fractions
20 containing the object compound were collected and evaporated under reduced pressure to give 4-(6-methoxyhexylthio)-piperidine (4.77 g). This compound was immediately used as the starting compound for the next step.

NMR (CD₃OD, δ): 1.30-1.90 (10H, m), 2.10-2.30 (2H, m),
2.60 (2H, t, J=7.30Hz), 3.31 (3H, s), 3.42 (2H, t,
25 J=4.28Hz)

APCI MASS (m/z): 232.4 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 98.

30

Preparation 125

4-(6-Methoxyhexylthiopiperidin-1-yl)benzonitrile

NMR (CDCl₃, δ): 1.30-1.50 (4H, m), 1.50-1.80 (6H, m),
1.95-2.15 (2H, m), 2.57 (2H, t, J=7.50Hz), 2.75-
35 3.10 (3H, m), 3.33 (3H, s), 3.37 (2H, t, J=6.32Hz),

3.65-3.90 (2H, m), 6.84 (2H, d, J=9.08Hz), 7.47
(2H, d, J=9.08Hz)

APCI MASS (m/z): 347 (M^+)

5 The following compound was obtained according to a
similar manner to that of Preparation 99.

Preparation 126

2-Amino-5-[4-[4-(6-methoxyhexylthio)piperidin-1-yl]-
10 phenyl]-1,3,4-thiadiazole

NMR (DMSO- d_6 , δ): 1.20-1.60 (10H, m), 1.85-2.05 (2H, m),
2.45-2.60 (2H, m), 2.80-3.00 (3H, m), 3.21 (3H, s),
3.29 (2H, t, J=6.42Hz), 3.60-3.80 (2H, m), 6.97
(2H, d, J=8.94Hz), 7.20 (2H, s), 7.55 (2H, d,
15 J=8.80Hz)

APCI MASS (m/z): 421 (M^+)

The following compound was obtained according to a
similar manner to that of Preparation 100.

20

Preparation 127

4-[2-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]-
phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
ethyl ester trifluoroacetic acid salt

25 ESI MASS (m/z)(Positive): 579 (M^+)

The following compound was obtained according to a
similar manner to that of Preparation 101.

30 Preparation 128

4-[2-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]-
phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]bezoic acid

NMR (CDCl₃, δ): 1.30-1.80 (10H, m), 1.95-2.25 (2H, m),
2.45-2.70 (2H, m), 2.70-3.20 (4H, m), 3.35 (3H, s),
35 3.35-3.50 (2H, m), 6.80-7.05 (3H, m), 7.36 (1H, s),

7.63 (1H, d, J=8.19Hz), 7.75 (1H, d, J=8.21Hz),
7.89 (1H, d, J=7.52Hz), 8.00-8.20 (2H, m)

APCI MASS (m/z): 551 (M^+)

- 5 The following compound was obtained according to a
similar manner to that of Preparation 102.

Preparation 129

4-[2-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]-
10 phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1772, 1603, 1535, 1470 cm^{-1}

Preparation 130

15 To a solution of tetrahydrothiopyran-4-one (1.0 g) in
dichloromethane (20 ml) was added 3-chloroperoxybenzoic acid
(4.16 g, purity 80%) under ice-cooling with stirring. The
mixture was stirred at the same temperature for 20 minutes
and then stirred at ambient temperature for 1 hour. The
20 resulting precipitates were filtered off, and the filtrate
was concentrated in vacuo. The residue was dissolved in a
mixture of ethyl acetate (50 ml) and water (20 ml) and
adjusted to pH 2 with 1N-hydrochloric acid. The organic layer
was separated, and the aqueous layer was extracted with ethyl
25 acetate (50 ml). The organic layers were combined, washed in
turn with water, saturated aqueous sodium bicarbonate and
saturated aqueous sodium chloride, dried over anhydrous
magnesium sulfate and evaporated in vacuo. The resulting
residue was dissolved in a mixture of dichloromethane (100
30 ml) and methanol (20 ml), dried over anhydrous magnesium
sulfate and evaporated in vacuo to give 1,1-
dioxotetrahydrothiopyran-4-one (1.18 g).

NMR (CD_3CD_2 , δ): 2.20 (4H, t, J=6.05Hz),
2.90-3.20 (4H, m)

Preparation 131

To a solution of (R,S)-5-hydroxy-2-phenyl-1,3-dioxane (5.0 g) (Acta Chemica Scandinavia, 1996; 50: 185-187) in DMF (50 ml) were added t-butyl dimethylsilyl chloride (12.5 g) and imidazole (9.45 g) with stirring at ambient temperature, and the mixture was allowed to stand at the same temperature overnight. The reaction mixture was poured into pH 6.86 standard buffer solution (500 ml) and extracted twice with ethyl acetate (200 ml). The extracts were combined, washed successively with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml) eluting with a mixture of n-hexane and ethyl acetate (9:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give (R,S)-5-(tert-butyl dimethylsilyloxy)-2-phenyl-1,3-dioxane (10.14 g).

NMR (CDCl₃, δ): 0.02-0.12 (6H, m), 0.89-0.94 (9H, m), 3.50-4.25 (5H, m), 5.50-5.95 (1H, m), 7.30-7.55 (5H, m)

ESI MASS (m/z) (Positive): 317.3 (M⁺+Na)

Preparation 132

A solution of (R,S)-5-tert-butyl dimethylsilyloxy-2-phenyl-1,3-dioxane (10.1g) and 10% palladium on carbon (50% including water) (5.0 g) in methanol (100 ml) was hydrogenated under an atmospheric pressure of hydrogen with stirring at ambient temperature for 2 hours. The catalyst was filtered off, and the filtrate was dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (300 ml), eluting with a mixture of n-hexane and ethyl acetate (3:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give (R,S)-2-(tert-butyl dimethylsilyloxy)-3-hydroxypropanol (5.69 g). This

compound was immediately used as the starting compound for the next step. To a solution of this compound were successively added diisopropylethylamine (14.4 ml) and acetyl chloride (6.5 ml) with stirring, and the mixture was stirred
5 at 0-5°C for 2 hours. Water (10 ml) was added to the reaction mixture, and the organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was dissolved in a mixture of methanol (100 ml) and
10 conc. hydrochloric acid (1.0 ml), and the solution was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated in vacuo and chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the object
15 compound were collected and evaporated under reduced pressure to give (R,S)-2-hydroxy-1,3-diacetoxypropane (2.06 g).

NMR (CDCl₃, δ): 2.06 (3H, s), 2.11 (3H, s), 3.74 (1H, m), 4.10-4.25 (4H, m)

20 Preparation 133

To a solution of oxalyl chloride (1.09 ml) in dichloromethane (20 ml) was added dropwise dimethylsulfoxide (DMSO) (1.93 ml) with stirring at -40~-50°C. After stirring at the same temperature for 5 minutes, to the solution was
25 added dropwise a solution of (R,S)-2-hydroxy-1,3-diacetoxypropane (2.0 g) in dichloromethane (20 ml) and stirred at the same temperature for 30 minutes. Triethylamine (5.54 ml) was added dropwise to the reaction mixture with stirring at the same temperature, and then the
30 mixture was stirred at ambient temperature for 30 minutes. The insoluble material was filtered off, and the filtrate was washed successively with 0.5N hydrochloric acid, water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and
35 evaporated in vacuo. The resulting residue was

chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (1:2 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 2-oxo-1,3-diacetoxyp propane

5 (1.17 g).

NMR (CDCl₃, δ): 2.18 (6H, s), 4.76 (4H, s)

ESI MASS (m/z)(Positive): 197.3 (M⁺+Na)

Preparation 134

10 To a solution of (R,S)-5-hydroxy-2-phenyl-1,3-dioxane (10.0 g) (Acta Chemica Scandinavica, 1996; 50: 185-187) in dichloromethane (200 ml) were added molecular sieves 4A powder (28 g) and pyridinium chlorochromic acid (PCC) (23.9 g) with stirring at ambient temperature and the mixture was
15 stirred at the same temperature for 2 hours. To the reaction mixture was added diethyl ether (100 ml), and the insoluble material was filtered off with celite and the filtrates were evaporated in vacuo. The residue was dissolved in a mixture of n-hexane (100 ml) and ethyl acetate (100 ml), dried over
20 anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (600 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 5-
25 oxo-2-phenyl-1,3-dioxane (7.06 g).

NMR (CDCl₃, δ): 4.49 (2H, s), 4.50 (2H, s), 5.90 (1H, s), 7.30-7.60 (5H, m)

Preparation 135

30 To a solution of 4-aminobutanol (630 mg), 5-oxo-2,2-dimethyl-1,3-dioxane (1.0 g) and acetic acid (1.20 ml) in MeOH (9 ml)-DMF (4 ml) was added sodium cyanoborohydride (622 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To the reaction
35 mixture was added dropwise a solution of allyloxycarbonyl

chloride (0.97 ml) in THF (2 ml) with stirring under ice-cooling, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added ethyl acetate (50 ml) and n-hexane (10 ml), and the solution was washed in turn with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of n-hexane and ethyl acetate (1:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-[allyloxycarbonyl-(2,2-dimethyl-1,3-dioxan-5-yl)]aminobutanol (1.04 g).

NMR (CDCl₃, δ): 1.42 (3H, s), 1.48 (3H, s), 1.50-1.80 (4H, m), 3.45 (2H, t, J=8.20Hz), 3.68 (2H, ABq, J=5.84 and 11.36Hz), 3.80-4.20 (5H, m), 4.50-4.70 (2H, m), 5.15-5.40 (2H, m), 5.80-6.05 (1H, m)

ESI MASS (m/z)(Positive): 310.3 (M⁺+Na)

Preparation 136

To a solution of oxalyl chloride (0.32 ml) in dichloromethane (10 ml) was added DMSO (0.57 ml) dropwise with stirring at -40~-50°C. After stirring at the same temperature for 5 minutes, to the solution was added dropwise a solution of 4-[allyloxycarbonyl(2,2-dimethyl-1,3-dioxan-5-yl)]aminobutanol (1.0 g) in dichloromethane (5 ml) and stirred at the same temperature for 30 minutes. Triethylamine (1.46 ml) was added dropwise to the reaction mixture with stirring at the same temperature, and then the mixture was stirred at ambient temperature for 30 minutes. The insoluble material was filtered off, and the filtrate was washed successively with 1N-hydrochloric acid, water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was dissolved in a mixture of acetic acid (16 ml) and water (4 ml), and the

solution was stirred at 90~100°C for 5 hours. The reaction mixture was concentrated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of dichloromethane and methanol (19:1 v/v). The fractions
5 containing the object compound were collected and evaporated under reduced pressure to give 4-[allyloxycarbonyl-(1,3-dihydropropan-2-yl)]aminobutylaldehyde (321 mg).

NMR (CDCl₃, δ): 1.50-1.75 (2H, m), 1.80-2.00 (2H, m),
2.40-2.60 (2H, m), 3.20-4.10 (7H, m), 4.59 (2H, d,
10 J=5.60Hz), 5.10-5.40 (2H, m), 5.80-6.10 (1H, m)
APCI MASS (m/z)(Positive): 246 (M⁺)

The following compound was obtained according to a similar manner to that of Preparation 95.

15

Preparation 137

N-t-Butoxycarbonyl-4-allyloxypiperidine

NMR (CDCl₃, δ): 1.45 (9H, s), 1.45-1.60 (2H, m),
1.70-1.95 (2H, m), 3.00-3.20 (2H, m), 3.40-3.60
20 (1H, m), 3.65-3.90 (2H, m), 3.95-4.05 (2H, m),
5.10-5.35 (2H, m), 5.80-6.10 (1H, m)

Preparation 138

To a solution of N-t-butoxycarbonyl-4-allyloxypiperidine
25 (2.95 g) in THF (15 ml) was added 9-borobicyclo[3.3.1]nonane
(9-BBN, 0.5M solution in THF) (51.3 ml) under ice-cooling
with stirring, and the mixture was stirred at ambient
temperature for 4 hours. The reaction mixture was cooled at
0-5°C, and 3M aqueous sodium hydroxide (20.4 ml) and 30%
30 hydrogen peroxide aqueous solution (20.4 ml) were added the
reaction mixture at 0-5°C. The mixture was stirred at
ambient temperature for 1 hour. To a reaction mixture was
added ethyl acetate (100 ml), and the solution was washed
successively with saturated aqueous sodium chloride, 1N-
35 hydrochloric acid, saturated aqueous sodium bicarbonate and

saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of dichloromethane and methanol (9:1 v/v).

- 5 The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(3-hydroxypropyloxy)-N-t-butoxycarbonylpiperidine (3.83 g).

NMR (CDCl₃, δ): 1.43 (9H, s), 1.43-1.60 (2H, m),
1.70-1.90 (4H, m), 2.35-2.45 (1H, m), 3.00-3.20
10 (2H, m), 3.35-3.55 (1H, m), 3.60-3.90 (5H, m)

Preparation 139

- To a solution of 4-(3-hydroxypropyloxy)-N-t-butyloxycarbonylpiperidine (3.82 g) in ethyl acetate (40 ml)
15 were added triethylamine (4.1 ml) and methanesulfonyl chloride (1.37 ml) with stirring under ice-cooling, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added water (50 ml) and ethyl acetate (50 ml) with stirring. The organic layer was
20 separated, washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (150 ml) eluting with a mixture of n-hexane and ethyl acetate (1:1 v/v). The fractions
25 containing the desired compound were collected and evaporated under reduced pressure to give 4-[3-(methanesulfonyloxy)-propyloxy]-N-t-butyloxycarbonylpiperidine (3.77 g).

NMR (CDCl₃, δ): 1.45 (9H, s), 1.45-1.60 (2H, m),
1.70-1.90 (2H, m), 1.90-2.10 (2H, m), 3.01 (3H, s),
30 3.03-3.20 (2H, m), 3.30-3.50 (1H, m), 3.57 (2H, t, J=5.87Hz), 3.65-3.80 (2H, m), 4.35 (2H, t, J=6.18Hz)

ESI MASS (m/z)(Positive): 360.3 (M⁺+Na)

Preparation 140

To a solution of 4-[3-(methanesulfonyloxy)propyloxy]-N-t-butyloxycarbonylpiperidine (3.76 g) in methanol (20 ml) was added 28% sodium methoxide methanol solution (22.7 ml), and the mixture was stirred under refluxing for 1.5 hours. The reaction mixture was evaporated in vacuo and dissolved in ethyl acetate (200 ml). The solution was washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(3-methoxypropyloxy)-N-t-butyloxycarbonylpiperidine (2.66 g).

NMR (CDCl₃, δ): 1.45 (9H, s), 1.45-1.60 (2H, m), 1.70-1.90 (4H, m), 3.00-3.15 (2H, m), 3.33 (3H, s), 3.35-3.60 (5H, m), 3.65-3.85 (2H, m)

ELSI MASS (m/z): 296.3 (M⁺+Na)

Preparation 141

A mixture of 1-acetyl-4-(4-hydroxyphenyl)piperazine (5.00 g) in N,N-dimethylformamide (50 ml) was treated with 1,6-dibromohexane (10.5 ml) and potassium carbonate (4.71 g), and the mixture was stirred for 18 hours at ambient temperature. To the reaction mixture was added water (200 ml), and the resulting precipitate was collected by filtration, washed with water and n-hexane successively and dried under reduced pressure to give crude 1-acetyl-4-[4-(6-bromohexyloxy)phenyl]piperazine (10.52 g), that was used in the next reaction directly.

MASS (m/z): 383 (M⁺+1)

Preparation 142

A solution of crude 1-acetyl-4-[4-(6-bromohexyloxy)-phenyl]piperazine (10.52 g) in methanol (105 ml) was treated

with 28% sodium methoxide in methanol (105 ml), and the solution was refluxed for 7 hours. After cooling, the precipitate was removed by filtration. The filtrate was added to a mixture of methylene chloride and water. The organic layer was taken, dried over magnesium sulfate, filtered and evaporated to give a crude oil. This oil in methylene chloride (20 ml) was treated with acetic anhydride (6.4 ml) under ice-cooling. After 6 hours, the solution was added to a mixture of methylene chloride and water. The organic layer was taken, dried over magnesium sulfate, filtered and evaporated. The residue was purified by silica gel column chromatography eluting with a mixed solvent of methylene chloride-methanol (from 0% to 3% gradient elution) to give 1-acetyl-4-[4-(6-methoxyhexyloxy)phenyl]piperazine (5.38 g) as a pale red solid.

NMR (DMSO- d_6 , δ): 1.24-1.78 (8H, m), 2.03 (3H, s), 2.86-3.06 (4H, m), 3.21 (3H, s), 3.23-3.36 (2H, m), 3.48-3.65 (4H, m), 3.87 (2H, d, $J=6.4\text{Hz}$), 6.82 (2H, dd, $J=9.2$ and 2.6Hz), 6.88 (2H, dd, $J=9.3$ and 2.6Hz)

MASS (m/z): 335 (M^++1)

Preparation 143

A mixture of 1-acetyl-4-[4-(6-methoxyhexyloxy)phenyl]piperazine (4.87 g) and 6N-hydrochloric acid (50 ml) was heated at 75°C for 3 hours. After cooling, the solution was adjusted to pH 11 with 25% sodium hydroxide aqueous solution then the resulting precipitate was collected by filtration, washed with water and dried under reduced pressure to give 4-[4-(6-methoxyhexyloxy)phenyl]piperazine (3.77 g) as a pale brown solid.

NMR (DMSO- d_6 , δ): 1.25-1.78 (8H, m), 2.74-2.96 (8H, m), 3.21 (3H, s), 3.30 (2H, t, $J=6.3\text{Hz}$), 3.86 (2H, t, $J=6.4\text{Hz}$), 6.79 (2H, d, $J=9.2\text{Hz}$), 6.83 (2H, d, $J=9.5\text{Hz}$)

MASS (m/z): 293 ($M^+ + 1$)

Preparation 144

A mixture of ethyl 4-fluorobenzoate (1.90 g) and 1-[4-(6-methoxyhexyloxy)phenyl]piperazine (3.00 g) in dimethylsulfoxide (45 ml) was treated with potassium carbonate (4.25 g), and the mixture was heated at 150°C for 22 hours. After cooling, water (200 ml) was added to the reaction mixture, and the resulting precipitate was collected by filtration, washed with water and dried under reduced pressure at 50°C for 7 hours to give ethyl 4-[4-[4-(6-methoxyhexyloxy)phenyl]piperazin-1-yl]benzoate (3.20 g) as another solid.

NMR (DMSO- d_6 , δ): 1.22-1.79 (8H, m), 1.33 (3H, t, $J=7.1\text{Hz}$), 3.08-3.20 (4H, m), 3.21 (3H, s), 3.27-3.40 (2H, m), 3.40-3.54 (4H, m), 3.88 (2H, t, $J=6.4\text{Hz}$), 4.24 (2H, q, $J=7.1\text{Hz}$), 6.83 (2H, d, $J=9.0\text{Hz}$), 6.94 (2H, d, $J=9.1\text{Hz}$), 7.04 (2H, d, $J=9.0\text{Hz}$), 7.81 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 441 ($M^+ + 1$)

Preparation 145

A mixture of ethyl 4-[4-[4-(6-methoxyhexyloxy)phenyl]piperazin-1-yl]benzoate (3.00 g) in ethanol (30 ml) was treated with 1N-sodium hydroxide aqueous solution (6.81 ml) then the mixture was refluxed for 24 hours, during which period tetrahydrofuran (20 ml) and 1N-sodium hydroxide aqueous solution (6.81 ml) was added. After cooling, water was added to the mixture, and the acidity of the mixture was adjusted to pH 1 with 1N-hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under reduced pressure to give 4-[4-[4-(6-methoxyhexyloxy)phenyl]piperazin-1-yl]benzoic acid dihydrochloride (2.25g) as another solid.

NMR (DMSO- d_6 , δ): 1.24-1.78 (8H, m), 3.04-3.21 (4H, m),

3.21 (3H, s), 3.30 (2H, t, J=6.3Hz), 3.34-3.56 (4H, m), 3.88 (2H, t, J=6.4Hz), 6.83 (2H, d, J=9.2Hz), 6.94 (2H, d, J=9.2Hz), 7.01 (2H, d, J=9.0Hz), 7.79 (2H, d, J=8.8Hz)

5 MASS (m/z): 413 ($M^+ + 1$)

Preparation 146

A mixture of 4-[4-[4-(6-methoxyhexyloxy)phenyl]-piperazin-1-yl]benzoic acid dihydrochloride (2.00 g) and 1-hydroxybenzotriazole (0.84 g) in methylene chloride (40 ml) was treated with triethylamine (1.44 ml) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, and the mixture was stirred for 24 hours at ambient temperature. The reaction mixture was added to water. The organic layer was taken, washed with saturated sodium hydrogen carbonate aqueous solution, water and saturated sodium chloride aqueous solution successively, and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. To the residue was added diisopropyl ether, and the resulting precipitate was filtered, washed with diisopropyl ether and dried under reduced pressure to give 4-[4-[4-(6-methoxyhexyloxy)phenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester (2.30 g) as a dark yellow solid.

25 NMR (CDCl_3 , δ): 1.33-1.87 (8H, m), 3.15-3.28 (4H, m), 3.34 (3H, s), 3.39 (2H, t, J=6.4Hz), 3.54-3.67 (4H, m), 3.93 (2H, t, J=6.5Hz), 6.87 (2H, d, J=9.3Hz), 6.95 (2H, d, J=9.3Hz), 7.00 (2H, d, J=9.1Hz), 7.37-7.58 (3H, m), 8.10 (1H, d, J=8.2Hz), 8.15 (2H, d, J=9.1Hz)

30 MASS (m/z): 530 ($M^+ + 1$)

Preparation 147

A mixture of 1-acetyl-4-(4-hydroxyphenyl)piperazine (3.00 g) in N,N-dimethylformamide was treated with 3-bromo-1-

propanol (1.60 ml) and potassium carbonate (2.82 g), and the mixture was heated at 60°C for 8 hours. Then 3-bromo-1-propanol (1.60 ml) was added again, and the mixture was heated at 110°C for 6 hours. After cooling, water and methylene chloride were added to the reaction mixture, and the organic layer was taken and dried over magnesium sulfate.

Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a mixed solvent of methylene chloride-methanol (from 0% to 6% gradient elution) to give 1-acetyl-4-[4-(3-hydroxypropyloxy)phenyl]piperazine (3.53 g) as a pale pink solid.

NMR (DMSO- d_6 , δ): 1.82 (2H, t, $J=6.3\text{Hz}$), 2.03 (3H, s), 2.84-3.06 (4H, m), 3.45-3.62 (4H, m), 3.95 (2H, t, $J=6.4\text{Hz}$), 4.13 (2H, t, $J=6.5\text{Hz}$), 4.47-4.60 (1H, m), 6.82 (2H, d, $J=9.2\text{Hz}$), 6.90 (2H, d, $J=9.3\text{Hz}$)

MASS (m/z): 279 (M^++1)

Preparation 148

A solution of 1-acetyl-4-[4-(3-hydroxypropyloxy)-phenyl]piperazine (3.47 g) in a mixed solvent of tetrahydrofuran (35 ml) and N,N-dimethylformamide (10 ml) was treated with silver(I) oxide (3.18 g) and 3-bromocyclohexene (1.86 ml), and the mixture was stirred at ambient temperature for 16 hours. To the mixture was added silver(I) oxide (3.18 g) and 3-bromocyclohexene (1.86 ml) again, and the mixture was heated at 60°C for 3 hours and then at 110°C for 40 hours. The precipitate was removed by filtration, and the filtrate was evaporated. The residue was purified by silica gel column chromatography eluting with a mixed solvent of methylene chloride-methanol (from 0% to 5% gradient solution) to give crude 1-acetyl-4-[4-[3-(2-cyclohexen-1-yloxy)propyloxy]phenyl]piperazine (1.60 g), that was used in the next reaction directly.

MASS (m/z): 359 (M^++1)

Preparation 149

A mixture of crude 1-acetyl-4-[4-[3-(2-cyclohexen-1-yloxy)propyloxy]phenyl]piperazine (1.55 g) in ethanol (16 ml) was hydrogenated at atmospheric pressure with 10% palladium-carbon (0.16 g) for 5 hours. After removal of catalyst by filtration, the filtrate was concentrated in vacuo to give crude 1-acetyl-4-[4-(3-cyclohexyloxypropyloxy)phenyl]-piperazine (1.18 g), that was used in the next reaction directly, as a brown oil.

MASS (m/z): 361 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 143.

Preparation 150

4-[4-(3-Cyclohexyloxypropyloxy)phenyl]piperazine

NMR ($CDCl_3$, δ): 1.12-1.94 (10H, m), 1.94-2.11 (2H, m), 3.03 (8H, s), 3.57-3.68 (1H, m), 3.86 (2H, t, $J=5.9$ Hz), 4.09 (2H, t, $J=5.9$ Hz), 6.86 (2H, d, $J=9.0$ Hz), 6.89 (2H, d, $J=9.0$ Hz)

APCI MASS (m/z): 319 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 144.

Preparation 151

Ethyl 4-[4-[4-(3-cyclohexyloxypropyloxy)phenyl]-piperazin-1-yl]benzoate

NMR ($CDCl_3$, δ): 1.12-1.95 (10H, m), 1.38 (3H, t, $J=7.1$ Hz), 1.95-2.14 (2H, m), 3.13-3.30 (4H, m), 3.42-3.56 (4H, m), 3.61 (2H, t, $J=6.2$ Hz), 3.81-3.94 (1H, m), 4.10 (2H, t, $J=5.9$ Hz), 4.34 (2H, q, $J=7.1$ Hz), 6.78-7.01 (6H, m), 7.95 (2H, d, $J=8.9$ Hz)

MASS (m/z): 467 ($M^+ + 1$)

Preparation 152

A mixture of ethyl 4-[4-[4-(3-cyclohexyloxypropyloxy)-phenyl]piperazin-1-yl]benzoate (290 mg) in the mixed solvent of tetrahydrofuran (15 ml) and ethanol (3 ml) was treated with 10% sodium hydroxide aqueous solution (0.50 ml), and the mixture was refluxed for 8 hours. After cooling, water was added to the reaction mixture, and the acidity of the mixture was adjusted to pH 1 with 1N-hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under reduced pressure to give 4-[4-[4-(3-cyclohexyloxypropyloxy)phenyl]piperazin-1-yl]benzoic acid dihydrochloride (96 mg) as a pale brown solid.

NMR (DMSO- d_6 , δ): 1.08-1.96 (12H, m), 3.07-3.62 (11H, m), 3.95 (2H, t, $J=5.5\text{Hz}$), 6.84 (2H, d, $J=9.1\text{Hz}$), 6.94 (2H, d, $J=9.2\text{Hz}$), 7.03 (2H, d, $J=8.9\text{Hz}$), 7.79 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 439 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 146.

Preparation 153

4-[4-[4-(3-Cyclohexyloxypropyloxy)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

MASS (m/z): 556 (M^++1)

Preparation 154

A solution of 4-bromo-2,6-dimethylphenol (2.00 g) and 1,7-dibromoheptane (5.10 g) in N,N-dimethylformamide (20 ml) was treated with potassium carbonate (2.06 g), and the mixture was stirred for 5 hours at ambient temperature. To the reaction mixture was added water and methylene chloride, and the organic layer was separated and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the

filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography eluting successively with the following solvents: (1) n-hexane, (2) n-hexane:ethyl acetate = 4:1, (3) n-hexane:ethyl acetate = 1:1. The
5 fractions containing the object compound were concentrated in vacuo to give crude 5-bromo-2-(7-bromoheptyloxy)-1,3-dimethylbenzene, that was used in the next reaction directly, as a pale yellow oil.

NMR (CDCl₃, δ): 1.28-1.98 (10H, m), 2.23 (6H, s),
10 3.35-3.50 (2H, m), 3.71 (2H, t, J=6.4Hz), 7.13 (2H, s)

Preparation 155

A solution of crude 5-bromo-2-(7-bromoheptyloxy)-1,3-dimethylbenzene (7.81 g) in methanol (78 ml) was treated with
15 28% sodium methoxide in methanol (78 ml), and the solution was refluxed for 8 hours. After cooling, the reaction mixture was evaporated under reduced pressure, and the residue was extracted with methylene chloride. The organic
20 layer was dried over magnesium sulfate and magnesium sulfate was filtered off, and then the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with a mixed solvent of n-hexane-ethyl acetate (from 0% to 7% gradient elution) to give
25 5-bromo-2-(7-methoxyheptyloxy)-1,3-dimethylbenzene (3.34 g) as a colorless oil.

NMR (CDCl₃, δ): 1.38-1.69 (8H, m), 1.69-1.89 (2H, m),
2.23 (6H, s), 3.35 (3H, s), 3.28-3.44 (2H, m),
3.65-3.78 (2H, m), 7.13 (2H, s)
30 MASS (m/z): 329 (M⁺+1)

Preparation 156

To a mixture of cesium carbonate (1.39 g), palladium(II) acetate (34.1 mg) and 2,2'-bis(diphenylphosphino)-1,1'-
35 binaphthyl (142 mg) in toluene (3.1 ml) was successively

added ethyl 4-(piperazin-1-yl)benzoate (0.85 g) and a solution of 5-bromo-2-(7-methoxyheptyloxy)-1,3-dimethylbenzene (1.00 g) in toluene (3 ml) in a stream of nitrogen. The mixture was stirred at ambient temperature for 5 30 minutes and refluxed for a further 20 hours. After cooling, the reaction mixture was concentrated in vacuo and to the residue was added water and methylene chloride. The organic layer was separated, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, 10 filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting successively with the following solvent: (1) n-hexane, (2) n-hexane:ethyl acetate = 9:1, (3) n-hexane:ethyl acetate = 5:1. The fractions containing the object compound were concentrated in 15 vacuo to give ethyl 4-[4-[4-(7-methoxyheptyloxy)-3,5-dimethylphenyl]piperazin-1-yl]benzoate (0.53 g) as a pale yellow solid.

NMR (CDCl₃, δ): 1.32-1.69 (11H, m), 1.69-1.88 (2H, m), 2.26 (6H, s), 3.17-3.30 (4H, m), 3.33 (3H, s), 3.38 20 (2H, t, J=6.5Hz), 3.41-3.54 (4H, m), 3.71 (2H, t, J=6.5Hz), 4.34 (2H, q, J=7.1Hz), 6.63 (2H, s), 6.91 (2H, d, J=9.0Hz), 7.95 (2H, d, J=9.0Hz)

MASS (m/z): 483 (M⁺+1)

25 The following compound was obtained according to a similar manner to that of Preparation 152.

Preparation 157

4-[4-[4-(7-Methoxyheptyloxy)-3,5-dimethylphenyl]- 30 piperazin-1-yl]benzoic acid dihydrochloride

NMR (DMSO-d₆, δ): 1.22-1.60 (8H, m), 1.60-1.79 (2H, m), 2.17 (6H, s), 3.10-3.50 (10H, m), 3.21 (3H, s), 3.64 (2H, t, J=6.3Hz), 6.65 (2H, s), 7.01 (2H, d, J=9.0Hz), 7.79 (2H, d, J=8.8Hz), 12.30 (1H, br s)

35 MASS (m/z): 455 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 146.

5 Preparation 158

4-[4-[4-(7-Methoxyheptyloxy)-3,5-dimethylphenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

NMR (CDCl₃, δ): 1.32-1.89 (10H, m), 2.27 (6H, s),
3.20-3.34 (4H, m), 3.34 (3H, s), 3.38 (2H, t,
10 J=6.5Hz), 3.54-3.68 (4H, m), 3.72 (2H, t, J=6.5Hz),
6.64 (2H, s), 7.00 (2H, d, J=9.1Hz), 7.37-7.62 (3H,
m), 8.09 (2H, d, J=8.3Hz), 8.15 (2H, d, J=9.0Hz)
MASS (m/z): 572 (M⁺+1)

15 The following compound was obtained according to a similar manner to that of Preparation 152.

Preparation 159

20 4-[4-(4-Cyclohexylpiperazin-1-yl)phenyl]benzoic acid dihydrochloride

NMR (DMSO-d₆, δ): 1.03-2.19 (10H, m), 2.80-2.93 (1H, m),
3.10-3.49 (8H, m), 7.08 (2H, d, J=8.4Hz), 7.65 (2H,
d, J=8.6Hz), 7.75 (2H, d, J=8.4Hz), 7.97 (2H, d,
J=8.3Hz)
25 MASS (m/z): 365 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 146.

30 Preparation 160

4-[4-(4-Cyclohexylpiperazin-1-yl)phenyl]benzoic acid benzotriazol-1-yl ester

NMR (CDCl₃, δ): 1.04-1.43 (6H, m), 1.69-2.04 (4H, m),
2.24-2.47 (1H, m), 2.68-2.88 (4H, m), 3.20-3.43
35 (4H, m), 7.03 (2H, d, J=8.8Hz), 7.38-7.66 (3H, m),

7.63 (2H, d, J=8.7Hz), 7.79 (2H, d, J=8.5Hz), 8.12
(1H, d, J=8.2Hz), 8.30 (2H, d, J=8.5Hz)

MASS (m/z): 482 ($M^+ + 1$)

5 Preparation 161

To a solution of methyl 4-(4-hydroxyphenyl)benzoate
(0.94 g), (S)-(-)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-
1-propanol (1.00 g) and triphenylphosphine (1.62 g) in N,N-
dimethylformamide (20 ml) was added dropwise diisopropyl
10 azodicarboxylate (1.21 ml) for 10 minutes under ice-cooling
in a stream of nitrogen. The solution was stirred for 16
hours at ambient temperature, and then water was added to the
reaction mixture, and the mixture was extracted with ethyl
acetate. The organic layer was washed with saturated aqueous
15 sodium chloride solution, dried over magnesium sulfate,
filtered and concentrated in vacuo. The residue was purified
by silica gel column chromatography eluting with a mixed
solvent of n-hexane-ethyl acetate (from 0% to 20% gradient
elution) to give methyl (S)-4-[4-[2-(tert-
20 butoxycarbonylamino)-3-cyclohexylpropyloxy]phenyl]benzoate
(290 mg) as a white solid.

NMR ($CDCl_3$, δ): 1.72-1.93 (13H, m), 1.46 (9H, s),
3.90-4.16 (3H, m), 3.93 (3H, s), 4.63-4.78 (1H, m),
6.93-7.05 (2H, m), 7.50-7.68 (4H, m), 8.06-8.15
25 (2H, m)

MASS (m/z): 368 ($M^+ + 2 - \text{Boc}$)

Preparation 162

A solution of methyl (S)-4-[4-[2-(tert-
30 butoxycarbonylamino)-3-cyclohexylpropyloxy]phenyl]benzoate
(0.28 g) in a mixed solvent of methanol (14 ml) and
tetrahydrofuran (3 ml) was treated with 1N-sodium hydroxide
aqueous solution, and the mixture was refluxed for 16 hours.
After cooling, water was added to the mixture, and the
35 acidity of the mixture was adjusted to pH 1 with 1N-

hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under reduced pressure to give (S)-4-[4-[2-(tert-butoxycarbonylamino)-3-cyclohexyl-propyloxy]phenyl]benzoic acid (222 mg) as a white solid.

- 5 NMR (DMSO- d_6 , δ): 0.66-1.48 (8H, m), 1.39 (9H, s),
1.48-1.87 (5H, m), 3.78-3.97 (3H, m), 6.79 (1H, d,
J=7.2Hzs), 7.04 (2H, d, J=8.8Hz), 7.68 (2H, d,
J=8.8Hz), 7.75 (2H, d, J=8.4Hz), 7.98 (2H, d,
J=8.4Hz), 12.83 (1H, br s)
10 MASS (m/z): 354 (M^+ +2-Boc)

The following compound was obtained according to a similar manner to that of Preparation 163.

15 Preparation 163

(S)-4-[4-[2-(tert-Butoxycarbonylamino)-3-cyclohexyl-propyloxy]phenyl]benzoic acid benzotriazol-1-yl ester

- NMR (CDCl₃, δ): 0.75-1.96 (13H, m), 1.47 (9H, s),
3.92-4.20 (3H, m), 4.60-4.79 (1H, m), 7.04 (2H, d,
20 J=8.8Hz), 7.40-7.63 (3H, m), 7.64 (2H, d, J=8.7Hz),
7.79 (2H, d, J=8.4Hz), 8.12 (1H, d, J=8.1Hz), 8.32
(2H, d, J=8.4Hz)
MASS (m/z): 571 (M^+ +1)

25 Preparation 164

- A mixture of 1-fluoro-4-nitrobenzene (2.71 ml), 1,2,3,6-tetrahydro-4-phenylpyridine hydrochloride (5 g) and potassium carbonate (8.83 g) in dimethylsulfoxide (50 ml) was stirred for 1 hour at 100°C. The reaction mixture was pulverized
30 with water. The precipitate was collected by filtration, and dried under reduced pressure to give 4-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)nitrobenzene.

IR (KBr): 1589.1, 1311.4, 1108.9 cm^{-1}

- NMR (CDCl₃, δ): 2.73-2.77 (2H, m), 3.73 (2H, t,
35 J=11.3Hz), 4.09 (2H, dd, J=2.5 and 5.9Hz), 6.16-

6.20 (1H, m), 6.80-6.88 (2H, m), 7.29-7.45 (5H, m),
8.12-8.20 (2H, m)

MASS (m/z): 281 ($M^+ + 1$)

5 Preparation 165

To a solution of 4-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)nitrobenzene (6.4 g) in ethyl alcohol (192 ml) and tetrahydrofuran (192 ml) was added 10% palladium on carbon (0.64 g), and hydrogen gas at atmosphere pressure for 6
10 hours. The reaction mixture was filtered through celite and evaporated under reduced pressure to give 1-(4-aminophenyl)-4-phenylpiperidine (5.66 g).

IR (KBr): 1604.5, 1511.9, 1382.7, 1207.2 cm^{-1}

15 NMR (CDCl_3 , δ): 1.84-1.97 (4H, m), 2.52-2.78 (3H, m),
3.10-3.73 (4H, m), 6.63-6.70 (2H, m), 6.84-6.92
(2H, m), 7.17-7.37 (5H, m)

MASS (m/z): 253 ($M^+ + 1$)

Preparation 166

20 To a solution of 1-(4-aminophenyl)-4-phenylpiperidine (2 g) in 47% hydrobromic acid (20 ml) and acetic acid (23 ml) was added dropwise sodium nitrite (0.55 g) in water (1 ml) under ice-cooling. The solution was then stirred for 30 minutes at 0°C. The reaction mixture was added dropwise
25 copper(I) bromide (2.27 g) in 47% hydrobromic acid (2.3 ml) under ice-cooling. The reaction mixture was then stirred for 1.5 hours at ambient temperature. The reaction mixture was pulverized with water. The precipitate was collected by filtration. The powder was added 1N-sodium hydroxide (21 ml)
30 and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica using dichloromethane/n-
35 hexane (1:1) as the elution to give 1-(4-bromophenyl)-4-

phenylpiperidine (1.23 g).

IR (KBr): 1583.3, 1488.8, 1382.7, 1214.9 cm^{-1}

NMR (CDCl_3 , δ): 1.77-1.96 (4H, m), 2.57-2.71 (1H, m),

2.74-2.88 (2H, m), 3.73-3.79 (2H, m), 6.81-6.89

5 (2H, m), 7.18-7.38 (7H, m)

MASS (m/z): 316 ($\text{M}^+ + 1$)

Preparation 167

A mixture of piperazine-1-carboxylic acid tert-butyl
10 ester (2.02 g), 1-(4-bromophenyl)-4-phenylpiperidine (2.86
g), tris(dibenzylidene acetone)(chloroform)-di-palladium(0)
(0.19 g), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
(0.28 g) and sodium tert-butoxide (1.74 g) in toluene (29 ml)
was stirred for 6 hours at 90°C. The reaction mixture was
15 added to a mixture of water and ethyl acetate. The organic
layer was taken and dried over magnesium sulfate. The
magnesium sulfate was filtered off, and the filtrate was
evaporated under reduced pressure. The residue was purified
by column chromatography over silica using
20 dichloromethane/methyl alcohol (50:1) as the elution to give
4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine-1-carboxylic
acid tert-butyl ester (2.93 g).

IR (KBr): 1691.3, 1596.8, 1116.6 cm^{-1}

NMR (CDCl_3 , δ): 1.48 (9H, s), 1.87-1.99 (4H, m),

25 2.60-2.90 (3H, m) 3.00-3.16 (4H, m), 3.55-3.71 (6H,

m), 6.87-6.99 (4H, m), 7.21-7.53 (5H, m)

MASS (m/z): 422 ($\text{M}^+ + 1$)

Preparation 168

30 To a solution of 4-[4-(4-phenylpiperidin-1-
yl)phenyl]piperazine-1-carboxylic acid tert-butyl ester (2.45
g) in 1,4-dioxane (62 ml) was added dropwise 4N-HCl/1,4-
dioxane (58 ml) at ambient temperature. The reaction mixture
was stirred for 110 minutes at ambient temperature, and
35 stirred for 2 hours at 80°C. The precipitate was filtered

and dried to give 1-[4-(4-phenylpiperidin-1-yl)phenyl]-piperazine trihydrochloride salt (2.07 g).

IR (KBr): 3494.4, 3237.9, 1635.3, 1498.4 cm^{-1}

NMR (DMSO- d_6 , δ): 1.98-3.90 (18H, m), 7.02-7.41 (7H, m),
5 7.82-7.86 (2H, m)

MASS (m/z): 322.4 ($M^+ + 1$) (free)

Preparation 169

A mixture of 4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine trihydrochloride salt (1.77 g) and 1N-sodium hydroxide (62 ml) in dichloromethane (62 ml) was stirred for 30 minutes at ambient temperature. The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the
15 filtrate was evaporated under reduced pressure to give 1-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine (1.19 g).

Preparation 170

A mixture of 4-fluorobenzoic acid ethyl ester (1.25 g),
20 1-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine (1.19 g) and potassium carbonate (1.53 g) in dimethylsulfoxide (18 ml) was stirred for 12 hours at 150°C. The reaction mixture was pulverized with water. The mixture was extracted with dichloromethane. The organic layer was separated, washed
25 with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica using dichloromethane/methyl alcohol (200:1) as the elution. The powder was recrystallized
30 from toluene (60 ml). The crystal was collected by filtration, and dried under reduced pressure to give 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (0.80 g).

IR (KBr): 1702.8, 1513.8, 1232.3 cm^{-1}

35 NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 1.89-2.00 (4H,

m), 2.55-2.84 (3H, m), 3.22-3.27 (4H, m), 3.46-3.51 (4H, m), 3.66-3.72 (2H, m), 4.34 (2H, q, J=7.1Hz), 6.90-7.03 (6H, m), 7.18-7.37 (5H, m), 7.93-7.98 (2H, m)

5 MASS (m/z): 470

Preparation 171

To a mixture of 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (0.78 g) in ethyl alcohol (39 ml) and 1,4-dioxane (39 ml) was added 10% NaOH aq. (1.3 ml) and refluxed for 16 hours. The reaction mixture was adjusted to pH 1-2 with 1N-HCl and the resulting precipitate was collected by filtration, and dried under reduced pressure to give 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride salt (0.65 g).

IR (KBr): 2840.6, 1670.1, 1602.6, 1232.3 cm⁻¹

NMR (CDCl₃+CD₃OD, δ): 2.05-2.20 (2H, m), 2.70-3.10 (3H, m), 3.40-3.85 (12H, m), 6.91-7.06 (4H, m), 7.25-7.37 (7H, m), 7.95-7.99 (2H, m)

20 MASS (m/z): 442 (free)

Preparation 172

To a suspension of 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride salt (0.62 g) and 1-hydroxybenzotriazole (0.2 g) in dichloromethane (12 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (0.22 g) and stirred for 22 hours at ambient temperature. The reaction mixture was added to a mixture of water and dichloromethane. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester (0.41 g).

IR (KBr): 1780.0, 1600.6, 1513.8, 1230.4 cm^{-1}

NMR (CDCl_3 , δ): 1.85-2.05 (4H, m), 2.60-2.90 (3H, m),
3.25-3.80 (10H, m), 6.95-7.55 (15H, m), 8.08-8.18
(2H, m)

5 MASS (m/z): 559 ($\text{M}^+ + 1$)

Preparation 173

To a suspension of 4-hydroxy-4-phenylpiperidine (5 g) and triethylamine (4.32 ml) in dichloromethane (50 ml) was
10 added dropwise di-tert-butylidicarbonate (6.16 g) in dichloromethane (6 ml) under ice-cooling. The reaction mixture was then stirred for 4 hours at ambient temperature. The reaction mixture was pulverized with water. The organic layer was separated, washed with brine, dried over magnesium
15 sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica using dichloromethane/methyl alcohol (30:1) as the elution to give 4-hydroxy-4-phenylpiperidine-1-carboxylic acid tert-butyl
20 ester (7.2 g).

IR (KBr): 3463.5, 1675.8, 1664.3, 1170.6 cm^{-1}

NMR (CDCl_3 , δ): 1.48 (9H, s), 1.63-2.08 (5H, m),
3.19-3.30 (2H, m), 3.90-4.10 (2H, m), 7.27-7.50
(5H, m)

25 MASS (m/z): 178 ($\text{M}^+ - \text{Boc} + 1$)

Preparation 174

To a solution of 4-hydroxy-4-phenylpiperidine-1-carboxylic acid tert-butyl ester (7.1 g) in N,N-
30 dimethylformamide (71 ml) was added 60% sodium hydride in mineral oil (1.13 g) under ice-cooling, and stirred for 1 hour at ambient temperature. The suspension was then stirred for 1.5 hours at 60°C. To the reaction mixture was added iodomethane (32 ml) at 40°C, and stirred for 30 minutes at
35 45°C. Water and ethyl acetate were added with stirring, and

the organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica
5 using n-hexane/ethyl acetate (4:1) as the elution to give 4-methoxy-4-phenylpiperidine-1-carboxylic acid tert-butyl ester (6.63 g).

IR (KBr): 1700.9, 1685.5, 1170.6 cm^{-1}

NMR (CDCl_3 , δ): 1.47 (9H, s), 1.79-2.05 (4H, m), 2.98

10 (3H, s), 3.12-3.24 (2H, m), 3.90-4.10 (2H, m),

7.28-7.39 (5H, m)

MASS (m/z): 192 ($\text{M}^+ - \text{Boc} + 1$)

Preparation 175

15 To a solution of 4-methoxy-4-phenylpiperidine-1-carboxylic acid tert-butyl ester (6.5 g) in ethyl acetate (65 ml) was added dropwise 4N-HCl/ethyl acetate (56 ml) at ambient temperature. The reaction mixture was stirred for 1.5 hours at ambient temperature. To the reaction mixture
20 was added diisopropyl ether. The precipitate was collected by filtration to give powder. The powder was adjusted to pH 11 with 1N-NaOH, and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off,
25 and the filtrate was evaporated under reduced pressure to give 4-methoxy-4-phenylpiperidine (3.47 g).

IR (KBr): 3322.7, 1535.1, 1070.3 cm^{-1}

NMR (CDCl_3 , δ): 1.80-2.07 (5H, m), 2.88-3.15 (7H, m),

7.28-7.44 (5H, m)

30 MASS (m/z): 192 ($\text{M}^+ + 1$)

Preparation 176

A mixture of 1-acetyl-4-(4-trifluoromethane-sulfonyloxyphenyl)piperazine (3 g), 4-methoxy-4-
35 phenylpiperidine (1.63 g), acetic acid palladium(II) salt

(0.11 g), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.42 g) and cesium carbonate (3.88g) in toluene (17 ml) was stirred for 30 minutes at ambient temperature. After being stirred for a further 17 hours at 100°C, the reaction mixture was diluted with dichloromethane. The suspension was filtered through celite, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica using ethyl acetate/methyl alcohol (30:1) as the elution to give 1-acetyl-4-[4-(4-methoxy-4-phenylpiperidin-1-yl)phenyl]piperazine (2.65 g).

IR (KBr): 1643.1, 1321.0, 1074.2 cm^{-1}
NMR (CDCl_3 , δ): 2.14 (3H, s), 2.14-2.17 (4H, m), 2.98 (3H, s), 2.98-3.45 (8H, m), 3.59-3.79 (4H, m), 6.92-7.00 (4H, m), 7.28-7.47 (5H, m)
MASS (m/z): 394 ($\text{M}^+ + 1$)

Preparation 177

A mixture of 1-acetyl-4-[4-(4-methoxy-4-phenylpiperidin-1-yl)phenyl]piperazine (2.5 g) and 10% NaOH aq. (10.2 ml) in ethyl alcohol (50 ml) was refluxed for 23.5 hours. The reaction mixture was evaporated under reduced pressure. The residue was washed with water, and dried to give 1-[4-(4-methoxy-4-phenylpiperidin-1-yl)phenyl]piperazine (2.18 g).

IR (KBr): 3290.0, 1513.8, 1232.3, 1074.2 cm^{-1}
NMR (DMSO-d_6 , δ): 1.91-2.11 (4H, m), 2.80-3.17 (11H, m), 3.20-3.45 (5H, m), 6.79-6.91 (4H, m), 7.25-7.46 (5H, m)
MASS (m/z): 352 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 178

4-[4-[4-(4-Methoxy-4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1702.8, 1511.9, 1236.1, 1105.0 cm^{-1}
NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 2.14-2.18 (4H, m), 3.01 (3H, s), 3.06-3.50 (12H, m), 4.34 (2H, q, $J=7.1\text{Hz}$), 6.90-7.03 (6H, m), 7.28-7.47 (5H, m),
5 7.93-7.98 (2H, m)
MASS (m/z): 500 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 170.

10 Preparation 179

4-[4-[4-(4-Methoxy-4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 2960.2, 1702.8, 1604.5, 1184.1 cm^{-1}

15 NMR ($\text{DMSO}-d_6$, δ): 2.20-3.70 (19H, m), 7.02-7.62 (11H, m), 7.78-7.83 (2H, m)

MASS (m/z): 472 (M^++1) (free)

The following compound was obtained according to a similar manner to that of Preparation 172.

20 Preparation 180

4-[4-[4-(4-Methoxy-4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

25 IR (KBr): 1762.6, 1600.6, 1230.4, 1184.1 cm^{-1}

NMR (CDCl_3 , δ): 2.10-2.20 (4H, m), 3.01 (3H, s), 3.05-3.64 (12H, m), 6.98-7.04 (6H, m), 7.32-7.51 (8H, m), 8.07-8.17 (3H, m)

MASS (m/z): 589 (M^++1)

30 The following compound was obtained according to a similar manner to that of Preparation 176.

Preparation 181

35 1-[4-[4-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)phenyl]-

piperazin-1-yl]ethanone

IR (KBr): 1648.8, 1637.3, 1334.5, 1230.4, 1099.2 cm^{-1} NMR (DMSO- d_6 , δ): 1.67-1.73 (4H, m), 2.03 (3H, s),

2.90-3.14 (8H, m), 3.50-3.60 (4H, m), 3.90 (4H, s),

6.86 (4H, s)

MASS (m/z): 346 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 177.

Preparation 182

8-(4-Piperazinylphenyl)-1,4-dioxo-8-azaspiro[4.5]decane

IR (KBr): 3284.2, 1513.8, 1328.7, 1110.8 cm^{-1} NMR (DMSO- d_6 , δ): 1.70 (4H, t, $J=5.7\text{Hz}$), 2.79-2.91 (8H,

m), 3.06-3.12 (4H, m), 3.25-3.38 (5H, m), 6.77-6.88 (4H, m)

MASS (m/z): 304 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 183

4-[4-[4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1704.8, 1511.9, 1224.6, 1108.9 cm^{-1} NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 1.86 (4H, t, $J=5.7\text{Hz}$), 3.20-3.25 (8H, m), 3.45-3.50 (4H, m),3.99 (4H, s), 4.34 (2H, q, $J=7.1\text{Hz}$), 6.89-6.93 (6H, m), 7.91-7.97 (2H, m)MASS (m/z): 452 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 171.

Preparation 184

4-[4-[4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 2962.1, 1670.1, 1321.0, 1230.4 cm^{-1}

5 NMR (DMSO-d_6 , δ): 1.70-2.00 (4H, m), 3.10-3.70 (16H, m),
7.00-7.20 (6H, m), 7.78-7.82 (2H, m)

MASS (m/z): 424 (M^++1) (free)

10 The following compound was obtained according to a
similar manner to that of Preparation 172.

Preparation 185

4-[4-[4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)phenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

15 IR (KBr): 1781.9, 1600.6, 1232.3 cm^{-1}

NMR (CDCl_3 , δ): 1.86 (4H, t, $J=5.7\text{Hz}$), 3.21-3.28 (8H, m),
3.59-3.64 (4H, m), 4.00 (4H, s), 6.95-7.02 (6H, m),
7.40-7.58 (3H, m), 8.07-8.17 (3H, s)

MASS (m/z): 541 (M^++1)

20

The following compound was obtained according to a
similar manner to that of Preparation 176.

Preparation 186

25 1-Acetyl-4-[4-(4-cyclohexyloxypiperidin-1-yl)phenyl]-piperazine

IR (KBr): 1621.8, 1236.1, 1101.2 cm^{-1}

NMR (CDCl_3 , δ): 1.20-2.00 (14H, m), 2.13 (3H, s),
2.75-3.78 (14H, m), 6.78-7.83 (4H, m)

30 MASS (m/z): 386 (M^++1)

Preparation 187

35 A mixture of 1-acetyl-4-[4-(4-cyclohexyloxypiperidin-1-yl)phenyl]piperazine (0.37 g) and 10% sodium hydroxide (1.9 ml) in ethyl alcohol (7.4 ml) was refluxed for 10 hours. The

reaction mixture was evaporated under reduced pressure. The residue was washed with water, and dried to give 1-[4-(4-cyclohexyloxypiperidin-1-yl)phenyl]piperazine (0.32 g).

- 5 The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 188

- 10 4-[4-[4-(4-Cyclohexyloxypiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1706.7, 1234.2, 1110.8 cm^{-1}

NMR (CDCl_3 , δ): 1.23-1.91 (17H, m), 2.77-2.86 (2H, m),
3.19-3.24 (4H, m), 3.30-3.60 (8H, m), 4.34 (2H, q,
J=7.1Hz), 6.89-6.93 (6H, m), 7.93-7.97 (2H, m)

- 15 MASS (m/z): 492 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 171.

20 Preparation 189

- 4-[4-[4-(4-Cyclohexyloxypiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 1672.0, 1322.9, 1230.4 cm^{-1}

- 25 NMR (DMSO-d_6 , δ): 1.00-2.20 (14H, m), 3.20-4.00 (14H, m), 6.80-8.00 (8H, m)

MASS (m/z): 464 ($\text{M}^+ + 1$) (free)

The following compound was obtained according to a similar manner to that of Preparation 172.

30

Preparation 190

- 4-[4-[4-(4-Cyclohexyloxypiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1781.9, 1600.6, 1513.8, 1230.4 cm^{-1}

- 35 NMR (CDCl_3 , δ): 1.13-2.10 (14H, m), 2.80-2.88 (2H, m),

3.22-3.64 (12H, m), 6.94-7.02 (6H, m), 7.39-7.58
(3H, m), 8.07-8.17 (3H, m)

MASS (m/z): 581 ($M^+ + 1$)

5 Preparation 191

To a suspension of 1-(4-hydroxyphenyl)piperazine (50 g) and potassium carbonate (46.5 g) in N,N-dimethylformamide (100 ml) was added dropwise benzyl chloroformate (47.86 g) at 0 to 10°C, and stirred for 4 hours at ambient temperature.

10 The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine and dried, and the solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (30:1)
15 to give 4-(4-hydroxyphenyl)piperazine-1-carboxylic acid benzyl ester (60.8 g).

IR (KBr): 3336.2, 1658.5, 1226.5 cm^{-1}

NMR (CDCl_3 , δ): 3.00 (4H, t, $J=4.9\text{Hz}$), 3.66 (4H, t, $J=5.1\text{Hz}$), 5.16 (2H, s), 5.29 (1H, s), 6.74-6.86
20 (4H, m), 7.30-7.40 (5H, m)

MASS (m/z): 313 ($M^+ + 1$)

Preparation 192

To a solution of 4-(4-hydroxyphenyl)piperazine-1-carboxylic acid benzyl ester (22.38 g) and pyridine (8.7 ml) in dichloromethane (336 ml) was added dropwise trifluoromethanesulfonic anhydride (15.7 ml) at 0 to 10°C, and stirred for 2 hours. The reaction mixture was washed successively with 0.5N hydrochloric acid, saturated sodium
30 hydrogen carbonate, water, brine, dried, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (50:1) to give 4-(4-trifluoromethanesulfonyloxyphenyl)piperazine-1-carboxylic acid benzyl ester (21.06 g).

35 IR (KBr): 1685.5, 1511.9, 1427.1 cm^{-1}

NMR (CDCl_3 , δ): 3.17 (4H, t, $J=5.0\text{Hz}$), 3.67 (4H, t, $J=5.2\text{Hz}$), 5.16 (2H, s), 6.87-7.18 (4H, m), 7.34-7.38 (5H, m)

MASS (m/z): 445 (M^++1)

5

The following compound was obtained according to a similar manner to that of Preparation 176.

Preparation 193

10 4-[4-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)phenyl]-piperazine-1-carboxylic acid benzyl ester

IR (KBr): 1697.1, 1519.6, 1230.4 cm^{-1}

NMR (CDCl_3 , δ): 1.85 (4H, t, $J=5.7\text{Hz}$), 3.00-3.05 (4H, m), 3.21 (4H, t, $J=5.7\text{Hz}$), 3.65 (4H, t, $J=5.1\text{Hz}$),
15 3.99 (4H, s), 5.16 (2H, s), 6.84-6.95 (4H, m), 7.36-7.39 (5H, m)

MASS (m/z): 438 (M^++1)

Preparation 194

20 To a solution of 4-[4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl]piperazine-1-carboxylic acid benzyl ester (30 g) in 1,4-dioxane (450 ml) was added 1N-hydrochloric acid (240 ml) at ambient temperature, and the mixture was stirred for 7 hours at 90°C. The reaction mixture was poured into water.
25 The mixture was adjusted to pH 10-12 with 1N-sodium hydroxide (480 ml), and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl
30 alcohol (50:1) to give 4-[4-(4-oxopiperidin-1-yl)phenyl]piperazine-1-carboxylic acid benzyl ester (21.22 g).

IR (KBr): 1718.3, 1683.6, 1232.3 cm^{-1}

NMR (CDCl_3 , δ): 2.55 (4H, t, $J=6.0\text{Hz}$), 3.05 (4H, t, $J=4.8\text{Hz}$), 3.49 (4H, t, $J=6.0\text{Hz}$), 3.66 (4H, t,

35

J=5.1Hz)

MASS (m/z): 394 ($M^+ + 1$)

Preparation 195

5 To a suspension of 4-(4-chlorophenyl)-4-hydroxypiperidine (8 g) and triethylamine (5.8 ml) in dichloromethane (80 ml) was added di-tert-butylidicarbonate (9.07 g) under ice-cooling. The suspension was then stirred for 5 hours at ambient temperature. The reaction mixture was
10 evaporated under reduced pressure. The residue was diluted with ethyl acetate and washed with water, washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography
15 over silica using n-hexane/ethyl acetate (3:1) as the elution to give 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylic acid tert-butyl ester (11.76 g).

IR (KBr): 3461.6, 1675.8, 1662.3, 1166.7 cm^{-1}

20 NMR (CDCl_3 , δ): 1.48 (9H, s), 1.62-2.04 (5H, m), 3.16-3.28 (2H, m), 3.97-4.09 (2H, m), 7.30-7.44 (4H, m)

MASS (m/z): 212 ($M^+ - \text{Boc}$)

25 The following compound was obtained according to a similar manner to that of Preparation 174.

Preparation 196

4-(4-Chlorophenyl)-4-methoxypiperidine-1-carboxylic acid tert-butyl ester

30 IR (KBr): 1695.1, 1423.2, 1170.6 cm^{-1}

NMR (CDCl_3 , δ): 1.47 (9H, s), 1.72-2.04 (4H, m), 2.97 (3H, s), 3.07-3.22 (2H, m), 3.90-4.04 (2H, m), 7.27-7.37 (4H, m)

MASS (m/z): 348.1 ($M^+ + \text{Na}$)

35

The following compound was obtained according to a similar manner to that of Preparation 175.

Preparation 197

5 4-(4-Chlorophenyl)-4-methoxypiperidine
IR (Film): 3305.4, 1490.7, 1135.9, 1072.2 cm^{-1}
NMR (CDCl_3 , δ): 1.75-2.03 (4H, m), 2.86-3.11 (8H, m),
 7.33 (4H, s)
MASS (m/z): 226.2

10

The following compound was obtained according to a similar manner to that of Preparation 164.

Preparation 198

15 1-(4-Nitrophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine
IR (KBr): 1594.8, 1319.1, 1066.4 cm^{-1}
NMR (CDCl_3 , δ): 1.91-2.20 (4H, m), 3.02 (3H, s), 3.34-
 3.48 (2H, m), 3.79-3.86 (2H, m), 6.83-6.91 (2H, m),
 7.29-7.39 (4H, m), 8.09-8.17 (2H, m)
20 MASS (m/z): 347.2

Preparation 199

A mixture of 1-(4-nitrophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine (8.9 g), iron powder (10.7 g) and ammonium
25 chloride (1.07 g) in ethanol (445 ml) and water (44.5 ml) was stirred at reflux for 5.5 hours. The insoluble material was filtered off, and the filtrate was evaporated under reduced pressure. To the residue was added a mixture of ethyl acetate (150 ml), water (100 ml) and saturated sodium
30 hydrogen carbonate (50 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. To the residue was added a mixture of diisopropyl ether (10 ml) and n-hexane (20 ml).
35 The precipitate was collected by filtration, and dried under

reduced pressure to give 1-(4-aminophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine (7.3 g).

IR (KBr): 3342.0, 1614.1, 1517.7, 1066.4 cm^{-1}

NMR (CDCl_3 , δ): 2.04-2.20 (4H, m), 2.99 (3H, s),

5 3.03-3.34 (6H, m), 6.64-6.70 (4H, m), 7.30-7.45
(4H, m)

MASS (m/z): 317.3

10 The following compound was obtained according to a
similar manner to that of Preparation 166.

Preparation 200

1-(4-Bromophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine

IR (KBr): 1589.1, 1494.6, 1249.6, 1062.6 cm^{-1}

15 NMR (CDCl_3 , δ): 1.96-2.15 (4H, m), 2.99 (3H, s), 3.08-

3.22 (2H, m), 3.40-3.55 (2H, m), 6.81-6.87 (2H, m),

7.30-7.38 (6H, m)

MASS (m/z): 382 ($\text{M}^+ + 1$)

20 The following compound was obtained according to a
similar manner to that of Preparation 167.

Preparation 201

25 4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-
yl]phenyl]piperazine-1-carboxylic acid tert-butyl ester

IR (KBr): 1695.1, 1511.9, 1234.2 cm^{-1}

NMR (CDCl_3 , δ): 1.48 (9H, s), 2.05-2.15 (4H, m), 2.99

(3H, s), 3.00-3.16 (6H, m), 3.37-3.43 (2H, m),

3.55-3.60 (4H, m), 6.87-6.99 (4H, m), 7.35 (4H, s)

30 MASS (m/z): 486 ($\text{M}^+ + 1$)

Preparation 202

To a solution of 4-[4-[4-(4-chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazine-1-carboxylic acid
35 tert-butyl ester (1.56 g) in ethyl acetate (62 ml) was added

dropwise 4N-HCl/ethyl acetate (40 ml) at ambient temperature.

The reaction mixture was stirred for 33 hours at ambient temperature. The precipitate was collected by filtration, and dried under reduced pressure to give 4-[4-[4-(4-chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]-piperazine trihydrochloride salt (1.52 g).

IR (KBr): 3382.5, 1504.2, 1255.4 cm^{-1}

NMR (DMSO_6 , δ): 2.24-3.76 (20H, m), 7.12-7.84 (8H, m)

MASS (m/z): 386 (free)

The following compound was obtained according to a similar manner to that of Preparation 169.

Preparation 203

4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazine

The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 204

4-[4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1702.8, 1602.6, 1513.8, 1234.2 cm^{-1}

MASS (m/z): 534 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 171.

Preparation 205

4-[4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 2962.1, 1697.1, 1602.6, 1515.8, 1224.6 cm^{-1}

MASS (m/z): 506 ($\text{M}^+ + 1$) (free)

The following compound was obtained according to a similar manner to that of Preparation 172.

Preparation 206

5 4-[4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1772.3, 1762.6, 1598.7, 1230.4, 1184.1 cm^{-1}

NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$, δ): 2.11-2.17 (3H, m), 3.01 (3H, s),

3.05-3.66 (12H, m), 6.95-7.04 (6H, m), 7.37-7.60

10 (7H, m), 8.07-8.17 (3H, m)

MASS (m/z): 623 ($M^+ + 1$)

Preparation 207

60% Sodium hydride (1.01 g) was added slowly to a
15 suspension of 4,4'-bicyclohexanol (5 g) in N,N-dimethylformamide (50 ml) at ambient temperature, and the mixture was stirred for 6 hours at 80°C. To the mixture was added dropwise n-propylbromide (2.29 ml) at 0-5°C, and the reaction mixture was stirred for 18.5 hours at 80°C. The
20 reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine and dried, and the solvent was evaporated under reduced pressure.

The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (50:1) to give
25 4'-propyl-4-hydroxy-1,1'-bicyclohexane (1.21 g).

IR (KBr): 3363.2, 1454.1, 1101.2 cm^{-1}

NMR (CDCl_3 , δ): 0.87-2.08 (24H, m), 2.88-3.60 (4H, m)

Preparation 208

30 To a solution of 4'-propoxybicyclohexyl-4-ol (1 g) and triethylamine (0.81 ml) in dichloromethane (10 ml) was added dropwise methanesulfonyl chloride (0.39 ml) at 0-5°C, and stirred for 3 hours. The reaction mixture was washed with water and brine, and dried, and evaporated under reduced
35 pressure to give 4'-propoxy-4-methylsulfonyloxy-1,1'-

bicyclohexane (1.44 g).

IR (KBr): 1454.1, 1351.9, 1338.4, 1164.8, 1110.8 cm^{-1}

NMR (CDCl_3 , δ): 0.87-2.20 (23H, m), 2.89-3.44 (7H, m)

5 Preparation 209

A mixture of 4-piperazinybenzoic acid ethyl ester (1.03 g), 4'-propoxy-4-methylsulfonyloxy-1,1'-bicyclohexane (1.4 g), potassium carbonate (0.91 g) in N,N-dimethylformamide (10 ml) was stirred for 8 hours at 130°C. The reaction mixture
10 was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine and dried, and the solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (200:1) to give 4-[4-(4'-
15 propoxy-1,1'-bicyclohexan-4-yl)piperazin-1-yl]benzoic acid ethyl ester (0.26 g).

IR (KBr): 1706.7, 1286.3, 1108.9 cm^{-1}

NMR (CDCl_3 , δ): 0.88-2.20 (26H, m), 3.00-3.67 (11H, m),
4.33 (2H, q, $J=7.1\text{Hz}$), 6.85-6.89 (2H, m), 7.92-7.97
20 (2H, m)

MASS (m/z): 455

The following compound was obtained according to a similar manner to that of Preparation 171.

25

Preparation 210

4-[4-(4'-Propoxy-1,1'-bicyclohexan-4-yl)piperazin-1-yl]benzoic acid hydrochloride

IR (KBr): 1695.1, 1228.4, 1112.7 cm^{-1}

30 NMR (CDCl_3 , δ): 0.88-2.03 (23H, m), 3.10-3.66 (12H, m),
6.86-6.91 (2H, m), 7.98-8.02 (2H, m)

MASS (m/z): 455

The following compound was obtained according to a
35 similar manner to that of Preparation 172.

Preparation 211

4-[4-(4'-Propoxy-1,1'-bicyclohexan-4-yl)piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

- 5 IR (KBr): 1772.3, 1695.1, 1226.5, 1187.9, 1089.6 cm^{-1}
NMR (CDCl_3 , δ): 0.88-2.04 (23H, m), 3.10-3.69 (12H, m),
6.93-6.98 (2H, m), 7.39-8.17 (6H, m)

Preparation 212

- 10 Lithium aluminum hydride (7.94 g) was added slowly to stirred tetrahydrofuran (80 ml) at ambient temperature. To the mixture was added dropwise 3,3-tetramethyleneglutamide (7 g) in tetrahydrofuran (70 ml) at ambient temperature. After refluxed for 5 hours, to the reaction mixture was added
15 dropwise water, and the mixture was filtered. The filtrate was evaporated under reduced pressure to give an oil (4.7 g). To the residue was added tetrahydrofuran (47 ml) and triethylamine (6.12 ml). To the mixture was added dropwise benzyloxycarbonyl chloride (5.76 g) in tetrahydrofuran (6 ml)
20 at ambient temperature. After stirring for 1.5 hours, the reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was separated, washed with diluted hydrochloric acid, water, brine, and dried, and evaporated under reduced pressure to give an oil (8.52 g).
25 The oil was chromatographed on a silica gel eluting with a mixture of dichloromethane and methyl alcohol (100:1) to give an oil (5.51 g). A solution of this oil (5.51 g) in methyl alcohol (55 ml) was added 10% palladium on carbon (0.55 g), and hydrogen gas at atmospheric pressure for 6 hours. The
30 reaction mixture was filtered through celite and evaporated under reduced pressure to give 8-azaspiro[4.5]decane (2.49 g).

- IR (KBr): 3249.5, 1531.2, 1467.6 cm^{-1}
NMR (CDCl_3 , δ): 1.40-1.64 (13H, m), 2.84 (4H, br s)
35 MASS (m/z): 140 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 176.

5 Preparation 213

1-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]ethanone

IR (KBr): 2937.1, 1648.8, 1515.8, 1238.1 cm^{-1}

10 NMR (CDCl_3 , δ): 1.42-1.67 (12H, m), 2.13 (3H, s), 3.03-3.08 (8H, m), 3.58-3.63 (2H, m), 3.73-3.79 (2H, m), 6.78-7.86 (4H, m)

MASS (m/z): 342 ($M^+ + 1$)

15 The following compound was obtained according to a similar manner to that of Preparation 177.

Preparation 214

8-(Piperazinylphenyl)-8-azaspiro[4.5]decane

20 The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 215

25 4-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1706.7, 1322.9, 1282.4, 1236.1, 1105.0 cm^{-1}

NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 1.41-1.65 (12H, m), 3.03-3.09 (4H, m), 3.19-3.24 (4H, m), 3.45-3.50 (4H, m), 4.34 (2H, q, $J=7.1\text{Hz}$), 6.89-6.94 (6H, m), 7.93-7.97 (2H, m)

30 MASS (m/z): 448 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 171.

Preparation 216

4-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 2946.7, 1689.3, 1388.5, 1226.5, 1184.1 cm^{-1}

5 NMR (DMSO-d_6 , δ): 1.40-2.40 (12H, m), 3.00-4.20 (12H, m), 7.01-7.15 (4H, m), 7.69-7.74 (2H, m), 7.78-7.83 (2H, m), 12.06 (1H, br s)

MASS (m/z): 420 ($\text{M}^+ + 1$) (free)

10 The following compound was obtained according to a similar manner to that of Preparation 172.

Preparation 217

15 4-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1781.9, 1598.7, 1513.8, 1228.4 cm^{-1}

NMR (CDCl_3 , δ): 1.43-1.73 (2H, m), 3.05-3.10 (4H, m), 3.22-3.27 (4H, m), 3.59-3.64 (4H, m), 6.90-7.02 (6H, m), 7.39-7.58 (3H, m), 8.07-8.17 (3H, m)

20 MASS (m/z): 537 ($\text{M}^+ + 1$)

Preparation 218

To a solution of 4-acetyl-1-(4-hydroxyphenyl)piperazine (20 g) and pyridine (11.02 ml) in dichloromethane (60 ml) was
25 added dropwise with stirring trifluoromethanesulfonic acid anhydride (20 ml) at 0°C . The mixture was then stirred for 1 hour at 0°C and 1 hour at room temperature. The reaction mixture was added to a mixture of 0.5 mol/l hydrochloric acid and dichloromethane. The organic layer was washed with
30 sodium hydrogen carbonate solution and sodium chloride solution. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (30:1
35 dichloromethane-methanol elution). Diisopropyl ether was

added to the residue, and precipitates were filtered, washed with the same solvent, and dried to give trifluoromethanesulfonic acid 4-(4-acetylpiperazin-1-yl)phenyl ester (27.78 g).

- 5 NMR (CDCl_3 , δ): 2.15 (3H, s), 3.20 (4H, m), 3.63 (2H, t, $J=5.2\text{Hz}$), 3.78 (2H, t, $J=5.2\text{Hz}$), 6.88-6.95 (2H, m), 7.15-7.20 (2H, m)
 MASS (m/z): 353 (M^++1)

10 Preparation 219

To a mixture of cesium carbonate (25.32 g), palladium(II) acetate (0.624 g) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (2.59 g) in toluene (110 ml) was successively added cis-2,6-dimethylmorpholine (8.21 ml) and trifluoromethanesulfonic acid 4-(4-acetylpiperazin-1-yl)phenyl ester (20 g) in stream of nitrogen. The mixture was stirred at ambient temperature for 30 minutes and at 100°C for further 12 hours. After cooling to room temperature, water was added to the reaction mixture.

- 15 The resulting precipitates were filtered, washed with water and dried. The residue was purified by silica gel chromatography (50:1 dichloromethane-methanol elution) to give 1-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]ethanone (7.78 g).

- 25 NMR (CDCl_3 , δ): 1.15-1.30 (6H, m), 2.13 (3H, s), 2.36 (2H, t, $J=11.1\text{Hz}$), 3.00-3.90 (12H, m), 6.85-7.00 (4H, m)
 MASS (m/z): 318 (M^++1)

30 Preparation 220

A mixture 1-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]ethanone (11.37 g) and 1.0 mol/l hydrochloric acid (225 ml) in ethanol (220 ml) was refluxed for 23 hours. The reaction mixture was added to a mixture of 1.0 mol/l sodium hydroxide solution and dichloromethane. The

- 35 1.0 mol/l sodium hydroxide solution and dichloromethane. The

organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give cis-2,6-dimethyl-4-(4-piperazinyphenyl)morpholine (3.64 g).

- 5 NMR (CDCl_3 , δ): 1.24 (6H, d, $J=6.3\text{Hz}$), 2.35 (2H, t, $J=11.1\text{Hz}$), 2.95-3.40 (11H, m), 3.70-3.9 (2H, m), 6.8-6.95 (4H, m)
 MASS (m/z): 276 (M^++1)

10 Preparation 221

- A solution of cis-2,6-dimethyl-4-(4-piperazinyphenyl)morpholine (2.00 g), 4-fluorobenzoic acid ethyl ester (1.43 g) and potassium carbonate (1.01 g) in dimethylsulfoxide (40 ml) was stirred for 8 hours at 150°C ,
15 during which period additional 4-fluorobenzoic acid ethyl ester (1.35 g) and potassium carbonate (1.0 g) was added to the mixture. The reaction mixture was added to a mixture of water and dichloromethane. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was
20 filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (25:1 dichloromethane-methanol elution) to give 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (2.5 g).

- 25 IR (KBr): 1705, 1697 1605, 1513, 1282, 1234 cm^{-1}
 NMR ($\text{DMSO}-d_6$, δ): 1.25 (6H, d, $J=6.3\text{Hz}$), 1.36 (3H, t, $J=7.1\text{Hz}$), 2.37 (2H, t, $J=11.1\text{Hz}$), 3.15-3.55 (10H, m), 3.7-3.9 (2H, m), 4.34 (2H, q, $J=7.1\text{Hz}$), 6.85-7.00 (6H, m), 7.95 (2H, d, $J=8.9\text{Hz}$)
30 MASS (m/z): 424 (M^++1)

Preparation 222

- A mixture of 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (2.46 g)
35 and 1.0 mol/l sodium hydroxide solution (11.6 ml) in a mixed

solvent of ethanol (50 ml) and tetrahydrofuran (125 ml) was refluxed for 33 hours, during which period additional 1.0 mol/l sodium hydroxide solution (24 ml) was added to the mixture. After cooling to ambient temperature, the reaction mixture was poured into cold water, and the mixture was adjusted to pH 2 with 1.0 mol/l hydrochloric acid. The resulting precipitates were filtered, washed with water and dried to give 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid (1.05 g).

IR (KBr): 1664, 1603, 1514, 1234 cm^{-1}

NMR (DMSO-d_6 , δ): 1.14 (6H, d, $J=6.2\text{Hz}$), 2.16 (2H, t, $J=11.0\text{Hz}$), 3.05-3.80 (12H, m), 6.80-7.15 (6H, m), 7.79 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 472 (M^++1)

Preparation 223

A mixture of 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid (1.01 g), 1-hydroxybenzotriazole (370 mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (986 mg) in methylene chloride (100 ml) was stirred for 4 hours at room temperature then evaporated under reduced pressure. Water was added to the residue and the resulting precipitate collected by filtration, washed with water, then dried under hi-vacuum to give 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester (1.197 g).

IR (KBr): 1784, 1603, 1512, 1232 cm^{-1}

NMR (CDCl_3 , δ): 1.26 (6H, d, $J=6.3\text{Hz}$), 2.38 (2H, t, $J=11.0\text{Hz}$), 3.15-3.45 (6H, m), 3.62 (4H, t, $J=5.1\text{Hz}$), 3.7-3.95 (2H, m), 6.8-7.1 (6H, m), 7.3-7.6 (3H, m), 8.0-8.25 (3H, m)

MASS (m/z): 589 (M^++1)

Preparation 224

To a mixture of cesium carbonate (6.33 g), palladium(II) acetate (156 mg) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (648 mg) in dioxane (28 ml) was successively added
5 cis-2,6-dimethyl-4-(4-piperazinyphenyl)morpholine (4.59 g) and 4'-trifluoromethanesulfonyloxy-1,1'-biphenyl-4-carboxylic acid methyl ester (5 g) in a stream of nitrogen. The mixture was stirred at ambient temperature for 30 minutes and at 80°C for a further 28 hours. After cooling to room temperature,
10 water was added to the reaction mixture. The resulting precipitates were filtered, washed with water and dried to give 4'-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]-piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid methyl ester (3.72 g).

15 NMR (CDCl₃, δ): 1.26 (6H, d, J=6.3Hz), 2.37 (2H, t, J=11.0Hz), 3.2-3.5 (10H, m), 3.75-3.9 (2H, m), 3.93 (3H, s), 6.8-7.15 (6H, m), 7.5-7.7 (4H, m), 8.07 (2H, d, J=8.3Hz)

MASS (m/z): 486 (M⁺+1)

Preparation 225

A mixture of 4'-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid methyl ester (3.70 g) and 1.0 mol/l sodium hydroxide solution
25 (30 ml) in a mixed solvent of methanol (75 ml) and tetrahydrofuran (185 ml) was refluxed for 15.5 hours. After cooling to ambient temperature, the reaction mixture was poured into cold water, and the mixture was adjusted to pH 2 with 1.0 mol/l hydrochloric acid. The resulting precipitates
30 were filtered, washed with water and diisopropyl ether and dried to give 4'-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid (3.68 g).

MASS (m/z): 472 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 226

5 4'-[4-[4-(2,6-Dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid benzotriazol-1-yl ester

NMR (DMSO-d₆, δ): 1.26 (6H, d, J=6.3Hz), 2.38 (2H, t, J=11.0Hz), 3.2-3.6 (10H, m), 3.7-3.95 (2H, m), 6.85-7.15 (6H, m), 7.4-7.9 (7H, m), 8.12 (2H, d, J=8.1Hz), 8.31 (2H, d, J=8.5Hz)

10 MASS (m/z): 589 (M⁺+1)

Preparation 227

A solution of 4-fluorobenzoic acid ethyl ester (3 g),
15 cis-2,6-dimethylmorpholine (2.26 g) and potassium carbonate (2.47 g) in dimethylsulfoxide (60 ml) was stirred for 18 hours at 80°C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was
20 filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (5:1 hexane-ethyl acetate elution) to give 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid ethyl ester (555 mg).

25 IR (KBr): 1695, 1605, 1518, 1244 cm⁻¹

NMR (CDCl₃, δ): 1.27 (6H, d, J=6.3Hz), 1.37 (3H, t, J=7.1Hz), 2.51 (2H, t, J=11.4Hz), 3.5-3.9 (4H, m), 4.33 (2H, q, J=7.1Hz), 6.85 (2H, d, J=9Hz), 7.93 (2H, d, J=8.9Hz)

30 MASS (m/z): 250 (M⁺+1)

Preparation 228

To a solution of 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid ethyl ester (0.55 g) in a mixed solvent of
35 methanol (3 ml) and tetrahydrofuran (6 ml) was added

hydrazine monohydrate (1.6 ml). The solution was refluxed for 20 hours, during which period additional hydrazine monohydrate (1.6 ml) was added to the mixture. After cooling to ambient temperature, the reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was washed with sodium chloride solution. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid hydrazide (489.7 mg).

IR (KBr): 1632, 1606, 1506, 1331, 1246 cm^{-1}

NMR (DMSO- d_6 , δ): 1.15 (6H, d, $J=6.1\text{Hz}$), 2.3 (2H, t, $J=11.4\text{Hz}$), 3.55-3.8 (4H, m), 4.36 (2H, br s), 6.94 (2H, d, $J=8.9\text{Hz}$), 7.71 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 250 ($M^+ + 1$)

Preparation 229

A mixture of 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid hydrazide (458 mg), 4-methoxycarbonylbzoyl chloride (622 mg) and pyridine (5 ml) in tetrahydrofuran (10 ml) was stirred for 6 hours at 0°C . The reaction mixture was added to water. The resulting precipitates were filtered, washed with water and dried to give 4-[N'-[4-(cis-2,6-dimethylmorpholin-4-yl)benzoyl]hydrazinocarbonyl]benzoic acid methyl ester (662.8 mg).

IR (KBr): 1724, 1606, 1279, 1242 cm^{-1}

NMR (DMSO- d_6 , δ): 1.17 (6H, d, $J=6.1\text{Hz}$), 2.35 (2H, t, $J=11.2\text{Hz}$), 3.6-3.85 (4H, m), 3.9 (3H, s), 7.02 (2H, d, $J=8.9\text{Hz}$), 7.83 (2H, d, $J=8.8\text{Hz}$), 8.0-8.2 (4H, m), 10.28 (1H, s), 10.58 (1H, s)

MASS (m/z): 412 ($M^+ + 1$)

Preparation 230

To a solution of 4-[N'-[4-(cis-2,6-dimethylmorpholin-4-yl)benzoyl]hydrazinocarbonyl]benzoic acid methyl ester (100

mg) in dimethoxyethane (3 ml) was added phosphorus pentasulfide (82 mg). The mixture was refluxed for 5 hours. After cooling to ambient temperature, the reaction mixture was poured into cold water and the mixture was adjusted to pH 11 with 1N-sodium hydroxide aqueous solution. The resulting precipitates were filtered, washed with water and dried to give 4-[5-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl][1,3,4]thiadiazol-2-yl]benzoic acid methyl ester (97.4 mg).

10 IR (KBr): 1716, 1605, 1437, 1412, 1277, 1238 cm^{-1}
NMR (CDCl_3 , δ): 1.29 (6H, d, $J=6.2\text{Hz}$), 2.54 (2H, t, $J=11.3\text{Hz}$), 3.61 (2H, d, $J=11.9\text{Hz}$), 3.7-3.9 (2H, m), 3.96 (3H, s), 6.96 (2H, d, $J=8.9\text{Hz}$), 7.91 (2H, d, $J=8.8\text{Hz}$), 8.0-8.25 (4H, m)
15 MASS (m/z): 410 (M^++1)

Preparation 231

A mixture of 4-[5-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl][1,3,4]thiadiazol-2-yl]benzoic acid methyl ester (527 mg) and 1.0 mol/l sodium hydroxide solution (2.6 ml) in a mixed solvent of methanol (10 ml) and tetrahydrofuran (25 ml) was refluxed for 6 hours. After cooling to ambient temperature, the reaction mixture was poured into cold water and the mixture was adjusted with 1.0 mol/l hydrochloric acid. The resulting precipitates were filtered, washed with water and dried to give 4-[5-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl][1,3,4]thiadiazol-2-yl]benzoic acid (429.1 mg).

IR (KBr): 1686, 1605, 1412, 1236 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 1.18 (6H, d, $J=6.1\text{Hz}$), 2.39 (2H, t, $J=11.2\text{Hz}$), 3.6-3.9 (4H, m), 7.11 (2H, d, $J=9.1\text{Hz}$), 7.87 (2H, d, $J=8.8\text{Hz}$), 8.11 (4H, s), 13.3 (1H, br s)
30 MASS (m/z): 396 (M^++1)

35 The following compound was obtained according to a

similar manner to that of Preparation 223.

Preparation 232

4-[5-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]-
5 [1,3,4]thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester
IR (KBr): 1780, 1603, 1441, 1414, 1230 cm^{-1}
NMR (CDCl_3 , δ): 1.3 (6H, d, $J=6.2\text{Hz}$), 2.45-2.65 (2H, m),
3.55-3.95 (4H, m), 6.97 (2H, d, $J=8.9\text{Hz}$), 7.4-7.7
(3H, m), 7.85-8.5 (7H, m)
10 MASS (m/z): 513 (M^++1)

Preparation 233

A mixture of cesium trichloride (5.0 g) in
tetrahydrofuran (45 ml) was stirred at room temperature for 6
15 hours. 1,4-Dioxaspiro[4.5]decan-8-one (1.4 g) was added to
the solution and stirred at room temperature for 1 hour. To
the solution was added dropwise with stirring
cyclohexylmagnesium chloride (2.0M solution in diethyl ether)
(6.7 ml) at 0°C . The reaction mixture was quenched with 10%
20 acetic acid aqueous solution. Diethyl ether was added to the
solution. The organic layer was taken, washed with brine,
sodium hydrogen carbonate solution, brine and dried over
magnesium sulfate. The magnesium sulfate was filtered off,
and the filtrate was concentrated under reduced pressure.
25 The residue was purified by silica gel chromatography to give
8-cyclohexyl-1,4-dioxaspiro[4.5]-decan-8-ol (1.266 g).

NMR (CDCl_3 , δ): 0.9-2.1 (19H, m), 3.85-4.05 (4H, m)

Preparation 234

30 To a solution of 8-cyclohexyl-1,4-dioxaspiro[4.5]decan-
8-ol (1.143 g) and iodomethane (0.59 ml) in N,N -
dimethylformamide (11 ml) was added sodium hydride (60%
dispersion in mineral oil) (342 mg) at 0°C . The solution was
stirred for 9 hours at 0°C , during which period additional
35 iodomethane (0.59 ml) and sodium hydride (60% dispersion in

mineral oil) (344 mg) was added to the mixture. The reaction mixture was added to a mixture of water and dichloromethane.

The organic layer was washed with water. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate elution) to give 8-cyclohexyl-8-methoxy-1,4-dioxaspiro[4.5]decane (1.201 g).

IR (NaCl): 1448, 1377, 1250 cm^{-1}

10 NMR (CDCl_3 , δ): 0.9-1.9 (19H, m), 3.11 (3H, s),
3.85-4.0 (4H, m)

MASS (m/z): 277 ($\text{M}^+ + \text{Na}$)

Preparation 235

15 A solution of 8-cyclohexyl-8-methoxy-1,4-dioxaspiro[4.5]decane (1.15g) and acetic acid (40 ml) in water was stirred at 100°C for 6 hours. After cooling to room temperature, the reaction mixture was added to a mixture of sodium hydrogen carbonate solution and diethyl ether. The organic layer was taken, washed with sodium hydrogen carbonate solution and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give 1-methoxy-1,1'-bicyclohexane-4-one (1.018 g).

20 NMR (CDCl_3 , δ): 0.8-2.7 (19H, m), 3.22 (3H, s)

MASS (m/z): 233 ($\text{M}^+ + \text{Na}$)

Preparation 236

To an ice cooled solution of ethyl 4-(piperazin-1-yl)benzoate (1.23 g) and 1-methoxy-1,1'-bicyclohexane-4-one (916 mg) in a mixed solvent of methanol (20 ml), tetrahydrofuran (15 ml) and acetic acid (0.74 ml) was added sodium cyanoborohydride (301 mg) in a stream of nitrogen. The mixture was stirred at this temperature for 1.5 hours and at room temperature for 7.5 hours. The reaction mixture was

quenched with saturated aqueous sodium hydrogen carbonate solution. Dichloromethane was added to the solution. The organic layer was taken, washed with sodium hydrogen carbonate solution and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (3:1 hexane-methanol elution) to give 4-[4-(1-methoxy-1,1'-bicyclohexan-4-yl)piperazinyl]benzoic acid ethyl ester (801 mg).

- 10 IR (KBr): 1701, 1608, 1520 cm^{-1}
NMR (CDCl_3 , δ): 0.7-1.9 (22H, m), 2.1-2.4 (1H, m),
2.65-2.85 (4H, m), 3.10 (3H, s), 3.25-3.4 (4H, m),
4.32 (2H, q, $J=7.1\text{Hz}$), 6.86 (2H, d, $J=8.8\text{Hz}$), 7.92
(2H, d, $J=8.9\text{Hz}$)
15 MASS (m/z): 429 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 231.

20 Preparation 237

4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazin-1-yl]benzoic acid

IR (KBr): 1689, 1610, 1232, 1186 cm^{-1}

MASS (m/z): 401 (M^++1)

25

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 238

30 4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazinyl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1782, 1603, 1522, 1232, 1186 cm^{-1}

NMR (CDCl_3 , δ): 0.7-2.1 (19H, m), 2.2-2.3 (1H, m),
2.7-2.9 (4H, m), 3.11 (3H, s), 3.4-3.55 (4H, m),
35 6.94 (2H, d, $J=9.1\text{Hz}$), 7.3-7.6 (3H, m), 8.0-8.2

(3H, m)

MASS (m/z): 518 ($M^+ + 1$)

The following compound was obtained according to a
5 similar manner to that of Preparation 236.

Preparation 239

4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazinyl]benzoic acid ethyl ester

10 IR (KBr): 1703, 1606, 1518, 1450, 1282, 1238 cm^{-1}
NMR (CDCl_3 , δ): 0.7-2.3 (23H, m), 2.55-2.7 (4H, m),
3.14 (3H, s), 3.25-3.45 (4H, m), 4.33 (2H, q,
J=7.1Hz), 6.8-6.95 (2H, m), 7.85-8.05 (2H, m)
MASS (m/z): 429 ($M^+ + 1$)

15

The following compound was obtained according to a
similar manner to that of Preparation 231.

Preparation 240

20 4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazinyl]-
benzoic acid

IR (KBr): 1668, 1603, 1228, 1186 cm^{-1}
MASS (m/z): 401 ($M^+ + 1$)

25

The following compound was obtained according to a
similar manner to that of Preparation 223.

Preparation 241

30 4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1767, 1603, 1524, 1232, 1186 cm^{-1}
NMR (CDCl_3 , δ): 0.7-2.1 (19H, m), 2.15-2.3 (1H, m),
2.55-2.7 (4H, m), 3.15 (3H, s), 3.35-3.55 (4H, m),
6.95 (2H, d, J=9.1Hz), 7.35-7.6 (3H, m), 8.0-8.2
35 (3H, m)

MASS (m/z): 518 ($M^+ + 1$)

Preparation 242

A solution of piperazine (30.37 g), 4-fluorobenzoic acid
5 ethyl ester (20 g) and potassium carbonate (65.75 g) in
dimethylsulfoxide (100 ml) was stirred for 5.5 hours at
150°C. After cooling to the room temperature, water was
added to the solution. The resulting precipitate was
collected by filtration and dried to give ethyl 4-
10 piperazinylbenzoate (18.48 g).

NMR ($CDCl_3$, δ): 1.37 (3H, t, $J=7.1$ Hz), 2.95-3.1 (4H, m),
3.2-3.4 (4H, m), 4.33 (2H, q, $J=7.1$ Hz), 6.87 (2H,
d, $J=9.0$ Hz), 7.85-8.0 (2H, m)

MASS (m/z): 235 ($M^+ + 1$)

15

The following compound was obtained according to a
similar manner to that of Preparation 236.

Preparation 243

20 4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
ethyl ester

IR (KBr): 1699, 1606, 1282, 1234, 1190 cm^{-1}

NMR ($CDCl_3$, δ): 0.85 (9H, s), 0.9-1.45 (8H, m), 1.75-
2.05 (4H, m), 2.1-2.4 (1H, m), 2.71 (4H, t,
25 $J=5.1$ Hz), 3.33 (4H, t, $J=5.1$ Hz), 4.25-4.4 (2H, m),
6.86 (2H, d, $J=9.0$ Hz), 7.85-8.0 (2H, m)

MASS (m/z): 373 ($M^+ + 1$)

The following compound was obtained according to a
30 similar manner to that of Preparation 231.

Preparation 244

4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid

IR (KBr): 1680, 1603 cm^{-1}

35 MASS (m/z): 345 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 223.

5 Preparation 245

4-4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1788, 1593, 1232 cm^{-1}

10 NMR (CDCl_3 , δ): 0.86 (9H, s), 0.9-1.4 (5H, m), 1.7-2.4
(5H, m), 2.75 (4H, t, $J=5.0\text{Hz}$), 3.47 (4H, t,
 $J=5.1\text{Hz}$), 6.8-7.05 (2H, m), 7.35-7.6 (3H, m), 8.0-
8.25 (3H, m)

MASS (m/z): 462 (M^++1)

15 The following compound was obtained according to a similar manner to that of Preparation 236.

Preparation 246

20 4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
ethyl ester

IR (KBr): 1701, 1606, 1282, 1248, 1192 cm^{-1}

25 NMR (CDCl_3 , δ): 0.84 (9H, s), 1.0-1.5 (10H, m), 1.9-2.25
(3H, m), 2.58 (4H, t, $J=5.1\text{Hz}$), 3.31 (4H, t,
 $J=5.1\text{Hz}$), 4.33 (2H, q, $J=7.1\text{Hz}$), 6.8-6.95 (2H, m),
7.85-8.0 (2H, m)

MASS (m/z): 373 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 231.

30

Preparation 247

4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid

IR (KBr): 1664, 1606, 1240 cm^{-1}

MASS (m/z): 345 (M^++1)

35

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 248

5 4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1778, 1603, 1232 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.86 (9H, s), 1.0-1.5 (7H, m),
1.95-2.3 (3H, m), 2.62 (4H, t, $J=5.1\text{Hz}$), 3.45 (4H,
t, $J=5.1\text{Hz}$), 6.95 (2H, d, $J=9.2\text{Hz}$), 7.35-7.6 (3H,
m), 8.05-8.2 (3H, m)

MASS (m/z): 462 (M^++1)

Preparation 249

15 A mixture of 4-bromo-4'-hydroxy-1,1'-biphenyl (5 g),
cis-2,6-dimethylmorpholine, dichlorobis(tri-o-
tolylphosphine)-palladium(II) and lithium
bis(trimethylsilyl)amide (1.0 M solution in hexanes) (44 ml)
in toluene (25 ml) was stirred for 6 hours at 100°C. The
20 reaction mixture was added to a mixture of 1.0 mol/l
hydrochloric acid and dichloromethane. The organic layer was
washed with 1.0 mol/l hydrochloric acid, sodium hydrogen
carbonate solution and sodium chloride solution. The organic
layer was taken and dried over magnesium sulfate. The
25 magnesium sulfate was filtered off, and the filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel chromatography (50:1 dichloromethane-
methanol elution) to give 4'-(cis-2,6-dimethylmorpholin-4-
yl)-1,1'-biphenyl-4-ol (1.49 g).

30 NMR (CDCl_3 , δ): 1.28 (6H, d, $J=6.3\text{Hz}$), 2.45 (2H, t,
 $J=11.2\text{Hz}$), 3.49 (2H, d, $J=10.6\text{Hz}$), 3.75-3.95 (2H,
m), 4.89 (1H, s), 6.8-7.0 (4H, m), 7.4-7.5 (4H, m)

MASS (m/z): 284 (M^++1)

35 The following compound was obtained according to a

similar manner to that of Preparation 218.

Preparation 250

Trifluoromethanesulfonic acid 4'-(cis-2,6-
5 dimethylmorpholin-4-yl)-1,1'-biphenyl-4-yl ester
NMR (CDCl₃, δ): 1.28 (6H, d, J=6.3Hz), 2.47 (2H, t,
J=11.3Hz), 3.52 (2H, d, J=10.4Hz), 3.7-3.95 (2H,
m), 6.98 (2H, d, J=8.8Hz), 7.30 (2H, d, J=8.8Hz),
7.48 (2H, d, J=8.7Hz), 7.60 (2H, d, J=8.8Hz)
10 MASS (m/z): 416 (M⁺+1)

Preparation 251

To a mixture of cesium carbonate (1.43 g), palladium(II)
acetate (35 mg) and 2,2'-bis(diphenylphosphino)-1,1'-
15 binaphthyl (146 mg) in dioxane (6 ml) was successively added
trifluoromethanesulfonic acid 4'-(cis-2,6-dimethylmorpholin-
4-yl)-1,1'-biphenyl-4-yl ester (1.30 g) and ethyl 4-
piperazinylbenzoate (0.88 g) in a stream of nitrogen. The
mixture was stirred at ambient temperature for 30 minutes and
20 at 100°C for further 6.5 hours. After cooling to room
temperature, water was added to the reaction mixture. The
resulting precipitates were filtered, washed with water and
dried. The residue was pulverized with acetone and collected
by filtration to give 4-[4-[4'-(cis-2,6-dimethylmorpholin-4-
25 yl)-1,1'-biphenyl-4-yl]piperazinyl]benzoic acid ethyl ester
(1.17 g).

IR (KBr): 1703, 1608, 1504, 1284, 1230 cm⁻¹

NMR (CDCl₃, δ): 1.28 (6H, d, J=6.3Hz), 1.38 (3H, t,
J=7.1Hz), 2.45 (2H, t, J=10.9Hz), 3.3-3.6 (10H, m),
30 3.7-3.95 (2H, m), 4.34 (2H, q, J=7.1Hz), 6.85-7.1
(6H, m), 7.45-7.6 (4H, m), 7.96 (2H, d, J=8.9Hz)

MASS (m/z): 500 (M⁺+1)

The following compound was obtained according to a
35 similar manner to that of Preparation 222.

Preparation 252

4-[4-[4'-(cis-2,6-Dimethylmorpholin-4-yl)-1,1'-biphenyl-4-yl]piperazinyl]benzoic acid

5 IR (KBr): 1668, 1603, 1504, 1230 cm^{-1}
MASS (m/z): 472 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 223.

10

Preparation 253

4-[4-[4'-(cis-2,6-Dimethylmorpholin-4-yl)-1,1'-biphenyl-4-yl]piperazinyl]benzoic acid benzotriazol-1-yl ester

15 IR (KBr): 1765, 1601, 1502, 1230, 1184 cm^{-1}
NMR (CDCl_3 , δ): 1.28 (6H, d, $J=6.3\text{Hz}$), 2.45 (2H, t, $J=11.2\text{Hz}$), 3.35-3.95 (12H, m), 6.9-7.1 (6H, m), 7.4-7.6 (7H, m), 8.05-8.2 (3H, m)
MASS (m/z): 589 ($\text{M}^+ + 1$)

20 Preparation 254

A solution of 4-bromophenol (3 g) and 1,4-dibromobutane (6.2 ml) in N,N-dimethylformamide (30 ml) was treated with potassium carbonate (2.89 g) at room temperature for 27 hours. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by silica gel chromatography (25:1 hexane-ethyl acetate elution) to give 1-bromo-4-(4-bromobutoxy)benzene (3.09 g).

25 NMR (CDCl_3 , δ): 1.8-2.15 (4H, m), 3.48 (2H, t, $J=6.4\text{Hz}$),
30 3.96 (2H, t, $J=5.9\text{Hz}$), 6.7-6.85 (2H, m), 7.3-7.45 (2H, m)

Preparation 255

35 A solution of 1-bromo-4-(4-bromobutoxy)benzene (3.05 g) in methanol (30 ml) was treated with 28% sodium methoxide in

methanol (2.43 ml), and the solution was refluxed for 5 hours. After cooling, the reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was washed with brine. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (10:1 hexane-ethyl acetate elution) to give 1-bromo-4-(4-methoxybutoxy)benzene (1.95 g).

10 IR (NaCl): 1591, 1489, 1286, 1244 cm^{-1}
NMR (CDCl_3 , δ): 1.65-1.95 (4H, m), 3.35 (3H, s), 3.44 (2H, t, $J=6.1\text{Hz}$), 3.95 (2H, t, $J=6.1\text{Hz}$), 6.77 (2H, d, $J=8.9\text{Hz}$), 7.36 (2H, d, $J=8.9\text{Hz}$)
MASS (m/z): 282 ($M^+ + \text{Na}$)

15

Preparation 256

To the solution of 1-bromo-4-(4-methoxybutoxy)benzene (4.94 g) and magnesium (463 mg) in tetrahydrofuran (50 ml) was added iodine at room temperature. The solution was refluxed for 7.5 hours, during which period diiodoethane was added to the mixture. After cooling to 0°C , 4-[4-(4-oxopiperidin-1-yl)phenyl]piperazine-1-carboxylic acid benzyl ester (4.94 g) in tetrahydrofuran (20 ml) was added dropwise with stirring to the solution. The mixture was stirred at room temperature for 2 hours. The reaction mixture was added to a mixture of ammonium chloride solution and ethyl acetate.

The organic layer was taken, washed with brine, sodium hydrogen carbonate solution and brine and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (50:1 dichloromethane-methanol elution) to give 4-[4-[4-hydroxy-4-[4-(4-methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (3.42 g).

35 NMR (CDCl_3 , δ): 1.65-2.0 (6H, m), 2.1-2.4 (2H, m),

2.95-3.3 (6H, m), 3.35 (3H, s), 3.35-3.75 (8H, m),
3.99 (2H, t, $J=5.9\text{Hz}$), 5.16 (2H, s), 6.8-7.05 (6H,
m), 7.3-7.5 (9H, m)

MASS (m/z): 574 (M^++1)

5

Preparation 257

To a solution of 4-[4-[4-hydroxy-4-[4-(4-methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (3.41 g) in dichloromethane (50 ml) was added trifluoroacetic acid (8.5 ml) at 0°C. The reaction mixture was stirred at 0°C for 1 hour and at room temperature for further 6 hours. To the reaction mixture was added 1 mol/ml sodium hydroxide solution (170 ml), dichloromethane (136 ml) and methanol (14 ml). The organic layer was washed with water and brine, dried over magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (50:1 dichloromethane-methanol elution) to give 4-[4-[4-[4-(4-methoxybutoxy)phenyl]-3,6-dihydro-2H-pyridin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (2.23 g).

IR (KBr): 1701, 1514, 1232 cm^{-1}

NMR (CDCl_3 , δ): 1.7-2.0 (4H, m), 2.65 (2H, br s), 2.95-3.15 (4H, m), 3.35 (3H, s), 3.35-3.9 (10H, m), 3.99 (2H, t, $J=6.0\text{Hz}$), 5.16 (2H, s), 6.18 (1H, m), 6.8-7.0 (6H, m), 7.3-7.45 (7H, m)

MASS (m/z): 556 (M^++1)

Preparation 258

To a mixture of 4-[4-[4-[4-(4-methoxybutoxy)phenyl]-3,6-dihydro-2H-pyridin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (2.20 g) and ammonium formate (1.25 g) in 90% methanol (44 ml) and dioxane was added 10% palladium on carbon at room temperature. The reaction mixture was heated at 100°C for 2 hours. After cooling, the reaction mixture

was filtered and evaporated. Sodium hydrogen carbonate solution was added to the residue. And the resulting precipitate was collected by filtration, washed with water and dried under hi-vacuum to give 1-[4-[4-[4-(4-methoxy-
5 butoxy)phenyl]piperidin-1-yl]phenyl]piperazine (1.36 g).

IR (KBr): 1514, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 1.5-1.9 (8H, m), 2.5-3.0 (7H, m), 3.23 (3H, s), 3.1-4.1 (11H, m), 6.8-7.25 (8H, m)

MASS (m/z): 424 ($M^+ + 1$)

10

The following compound was obtained according to a similar manner to that of Preparation 221.

Preparation 259

15 4-[4-[4-[4-(4-Methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid methyl ester

IR (KBr): 1711, 1606, 1514, 1282, 1227 cm^{-1}

NMR (CDCl_3 , δ): 1.38 (3H, t, $J=7.1\text{Hz}$), 1.65-2.0 (8H, m),
2.5-2.9 (3H, m), 3.5-3.8 (12H, m), 3.35 (3H, s),
20 3.97 (2H, t, $J=6.0\text{Hz}$), 4.34 (2H, q, $J=7.0\text{Hz}$), 6.8-
7.2 (10H, m), 7.95 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 572 ($M^+ + 1$)

25 The following compound was obtained according to a similar manner to that of Preparation 222.

Preparation 260

30 4-[4-[4-[4-(4-Methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid

IR (KBr): 1514, 1228 cm^{-1}

MASS (m/z): 544 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 223.

35

Preparation 261

4-[4-[4-[4-(4-Methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1514, 1230 cm^{-1}

5 NMR (CDCl_3 , δ): 1.6-2.0 (8H, m), 2.5-2.9 (3H, m),
3.2-3.8 (15H, m), 3.9-4.05 (2H, m), 6.8-7.3 (10H, m), 7.35-7.6 (3H, m), 8.05-8.25 (3H, m)

MASS (m/z): 661 ($\text{M}^+ + 1$)

10 The following compound was obtained according to a similar manner to that of Preparation 219.

Preparation 262

15 1-[4-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazin-1-yl]ethanone

IR (KBr): 1622, 1516, 1448, 1242 cm^{-1}

NMR (CDCl_3 , δ): 1.3-1.9 (10H, m), 1.95-2.15 (5H, m), 2.57 (2H, t, $J=7.3\text{Hz}$), 2.6-2.85 (3H, m), 2.95-3.15 (4H, m), 3.25-3.85 (11H, m), 6.89 (4H, s)

20 MASS (m/z): 434 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 220.

Preparation 263

25 1-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazine

IR (KBr): 1622, 1514, 1454, 1242, 1120 cm^{-1}

30 NMR (CDCl_3 , δ): 1.3-1.9 (10H, m), 1.95-2.15 (2H, m),
2.57 (2H, t, $J=7.3\text{Hz}$), 2.6-2.85 (3H, m), 3.04 (8H, s), 3.3-3.6 (7H, m), 6.89 (4H, s)

MASS (m/z): 392 ($\text{M}^+ + 1$)

35 The following compound was obtained according to a similar manner to that of Preparation 221.

Preparation 264

4-[4-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid ethyl ester

5 NMR (CDCl₃, δ): 1.3-1.9 (13H, m), 1.95-2.15 (2H, m),
2.57 (2H, t, J=7.3Hz), 2.6-2.85 (3H, m), 3.15-3.6
(15H, m), 4.34 (2H, q, J=7.0Hz), 6.85-7.0 (6H, m),
7.95 (2H, d, J=8.8Hz)

MASS (m/z): 540 (M⁺+1)

10

The following compound was obtained according to a similar manner to that of Preparation 222.

Preparation 265

15 4-[4-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid

IR (KBr): 1605, 1587, 1546, 1514, 1408, 1225 cm⁻¹

MASS (m/z): 512 (M⁺+1)

20

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 266

25 4-[4-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1782, 1601, 1514; 1446, 1230, 1184 cm⁻¹

NMR (CDCl₃, δ): 1.3-1.9 (10H, m), 1.95-2.15 (2H, m),
2.58 (2H, t, J=7.3Hz), 2.65-2.85 (3H, m), 3.15-3.7
(15H, m), 6.85-7.1 (6H, m), 7.35-7.6 (3H, m), 8.05-
30 8.2 (3H, m)

MASS (m/z): 629 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 254.

35

Preparation 267

4-(4-Bromobutoxy)benzonitrile

IR (KBr): 2222, 1605, 1506, 1302, 1252 cm^{-1} NMR (CDCl_3 , δ): 1.9-2.2 (4H, m), 3.49 (2H, t, $J=6.2\text{Hz}$),
5 4.05 (2H, t, $J=5.7\text{Hz}$), 6.85-7.0 (2H, m), 7.5-7.65
(2H, m)MASS (m/z): 254 (M^+)

10 The following compound was obtained according to a
similar manner to that of Preparation 256.

Preparation 268

4-(4-Methoxybutoxy)benzonitrile

IR (KBr): 2216, 1605, 1570, 1510, 1468, 1308, 1261 cm^{-1} NMR (CDCl_3 , δ): 1.65-2.0 (4H, m), 3.35 (3H, s), 3.44
15 (2H, t, $J=6.1\text{Hz}$), 4.00 (2H, t, $J=6.2\text{Hz}$), 6.85-7.0
(2H, m), 7.5-7.65 (2H, m)MASS (m/z): 206 (M^++1)Preparation 269

20 To a solution of 4-(4-methoxybutoxy)benzonitrile (21.8
g) and trifluoroacetic acid (109 ml) in toluene (218 ml) was
added thiosemicarbazide (11.62 g). The solution was stirred
for 31 hours at 60°C, during which period additional
25 thiosemicarbazide (2.90 g) and trifluoroacetic acid was added
to the mixture. The reaction mixture was pulverized with
ethyl acetate. The precipitate was collected by filtration
and dried to give 5-[4-(4-methoxybutoxy)phenyl]-
[1,3,4]thiadiazol-2-ylamine trifluoroacetic acid salt (15.10
30 g).

IR (KBr): 1674, 1606, 1400 cm^{-1} NMR (CDCl_3 , δ): 1.55-2.0 (4H, m), 3.36 (3H, s), 3.45
(2H, t, $J=6.0\text{Hz}$), 4.04 (2H, t, $J=6.1\text{Hz}$), 4.41 (4H,
br s), 6.95 (2H, d, $J=8.7\text{Hz}$), 7.63 (2H, d, $J=8.7\text{Hz}$)MASS (m/z): 280
35

Preparation 270

To a suspension of 5-[4-(4-methoxybutoxy)phenyl]-
[1,3,4]thiadiazol-2-ylamine trifluoroacetic acid salt (45.00
5 g) in ethanol (450 ml) was added ethyl 4-bromoacetylbenzoate
(28.85g), and the mixture was stirred under reflux for 4
hours. The reaction mixture was pulverized with ethyl
acetate. The precipitate was collected by filtration and
dried. To a suspension of the powder in xylene (450 ml) was
10 added trifluoroacetic acid (67.5 ml), and the mixture was
stirred at 130°C for 4 hours. The reaction mixture was
pulverized with diisopropyl ether. The precipitate was
collected by filtration and dried. The residue was
pulverized with ethyl acetate, and the precipitate was
15 collected by filtration and dried to give 4-[2-[4-(4-
methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-
yl]benzoic acid ethyl ester (29.85 g).

NMR (CDCl₃, δ): 1.41 (3H, t, J=7.1Hz), 1.65-2.0 (4H, m),
3.36 (3H, s), 3.4-3.55 (2H, m), 4.0-4.15 (2H, m),
20 4.39 (2H, q, J=7.1Hz), 6.99 (2H, d, J=8.8Hz), 7.55-
8.15 (7H, m)

MASS (m/z): 452 (M⁺+1)

The following compound was obtained according to a
25 similar manner to that of Preparation 231.

Preparation 271

4-[2-[4-(4-Methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]-
thiadiazol-6-yl]benzoic acid

30 IR (KBr): 1680, 1608, 1591, 1549, 1468, 1404, 1257 cm⁻¹

NMR (DMSO-d₆, δ): 1.55-1.9 (4H, m), 3.24 (3H, s),
3.3-3.5 (2H, m), 4.10 (2H, t, J=5.9Hz), 7.14 (2H,
d, J=8.7Hz), 7.8-8.05 (6H, m), 8.84 (1H, s)

MASS (m/z): 424 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 272

5 4-[2-[4-[4-Methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]-
thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester
IR (KBr): 1768, 1606, 1547, 1470, 1404, 1255, 1176 cm^{-1}
NMR (CDCl_3 , δ): 1.6-2.0 (4H, m), 3.37 (3H, s), 3.47 (3H,
t, $J=6.0\text{Hz}$), 4.08 (3H, t, $J=6.1\text{Hz}$), 7.02 (2H, d,
10 $J=8.7\text{Hz}$), 7.4-7.65 (3H, m), 7.7-8.4 (8H, m)
MASS (m/z): 541 (M^++1)

Preparation 273

A solution of oxalyl dichloride (597 μl) in dry
15 dichloromethane (7 ml) was cooled to -70°C in nitrogen
atmosphere, and a solution of dimethylsulfoxide (1.15 ml) in
dry dichloromethane (1.5 ml) was added slowly and stirred for
30 minutes at -70°C . To the reaction mixture was added a
solution of (3-hydroxypropyl)carbamic acid tert-butyl ester
20 (1.0 g) in dry dichloromethane (7 ml) slowly to maintain the
reaction temperature at -60°C and stirred for 30 minutes at
 -70°C . To the reaction mixture was added triethylamine (3.98
ml) slowly to maintain the reaction temperature at -60°C .
Then the reaction mixture was allowed to warm to room
25 temperature. To the reaction mixture was added water (10 ml)
and stirred for 10 minutes, then the organic layer was
separated. The aqueous layer was extracted with
dichloromethane (50 ml x 2). The organic layer was combined
and washed with brine, dried over magnesium sulfate.
30 Magnesium sulfate was filtered off, and the filtrate was
evaporated under reduced pressure to give 3-tert-
butoxycarbonylaminopropionaldehyde (1.28 g), that was used
crude in the next reaction.

35 The following compound was obtained according to a

similar manner to that of Preparation 273.

Preparation 274

5-tert-Butoxycarbonylaminovaleraldehyde, that was used
5 crude in the next reaction.

The following compound was obtained according to a
similar manner to that of Preparation 273.

10 Preparation 275

6-tert-Butoxycarbonylaminoheptanaldehyde, that was used
crude in the next reaction.

The following compound was obtained according to a
15 similar manner to that of Preparation 273.

Preparation 276

4-tert-Butoxycarbonylaminobutylaldehyde, that was used
crude in the next reaction.

20

Preparation 277

To an ice-cooled solution of 5-aminopentan-1-ol (5.0 g)
in water (40 ml) and acetone (40 ml) was added triethylamine
(8.78 g) and di-tert-butyl dicarbonate (13.75 g), then the
25 solution was stirred at 30°C for 3 hours. The solvent was
evaporated under reduced pressure and extracted with ethyl
acetate. The organic layer was washed with water and brine,
then dried over magnesium sulfate. Magnesium sulfate was
filtered off, and the filtrate was evaporated under reduced
30 pressure to give a crude yellow oil (12.7 g). The crude oil
was purified by silica gel chromatography (50:1 - 4:1
dichloromethane-methanol) to give 5-hydroxypentylcarbamic
acid tert-butyl ester (8.68 g), as a pale yellow oil.

IR (KBr): 3344.0, 2975.6, 2935.1, 2865.7, 1706.7,
35 1695.1, 1529.3, 1280.5, 1249.6, 1178.3,

1168.7 cm^{-1}

NMR (DMSO-d_6 , δ): 1.1-1.6 (15H, m), 2.88 (2H, dd, $J=6.5$ and 12.6Hz), 3.2-3.5 (2H, m), 4.33 (1H, t, $J=5.1\text{Hz}$), 6.75 (1H, m)

5

The following compound was obtained according to a similar manner to that of Preparation 277.

Preparation 278

10

6-Hydroxyhexylcarbamic acid tert-butyl ester

IR (KBr): 3351.7, 2977.6, 2937.1, 2859.9, 1714.4, 1679.7, 1533.1, 1276.6, 1249.6, 1180.2, 1164.8 cm^{-1}

15

NMR (DMSO-d_6 , δ): 1.0-1.6 (17H, m), 4.83 (2H, dd, $J=6.5$ and 12.8Hz), 3.2-3.59 (2H, m), 4.32 (1H, t, $J=5.2\text{Hz}$), 6.75 (1H, m)

The following compound was obtained according to a similar manner to that of Preparation 277.

20

Preparation 279

(S)-(-)-4-tert-Butoxycarbonylamino-2-hydroxybutyric acid

NMR (DMSO-d_6 , δ): 1.37 (9H, s), 1.4-1.9 (2H, m), 3.00 (2H, dd, $J=7.0$ and 13.3Hz), 3.92 (1H, dd, $J=4.0$ and 8.4Hz), 6.78 (1H, m)

25

Preparation 280

To a solution of pyridinium chlorochromate (2.0 g) in dichloromethane (15 ml) was added a solution of 6-hydroxyhexanoic acid ethyl ester (1.0 g) in dichloromethane (1.5 ml) in one portion and stirred for 1.5 hours at ambient temperature. Ether (15 ml) was added to the reaction mixture, and the insoluble material removed by filtration and discarded. The filtrate was purified by silica gel chromatography (diethyl ether) to give 6-oxohexanoic acid

35

ethyl ester (884.6 mg), as a pale green oil.

IR (KBr): 2981.4, 2940.9, 2871.5, 2827.1, 2723.0,
1731.8, 1184.1 cm^{-1}

NMR (CDCl_3 , δ): 1.26 (3H, t, $J=7.1\text{Hz}$), 1.5-1.8 (4H, m),
2.2-2.6 (4H, m), 4.13 (2H, q, $J=7.1\text{Hz}$), 9.77 (1H,
t, $J=1.6\text{Hz}$)

The following compound was obtained according to a
similar manner to that of Preparation 280.

Preparation 281

9-Oxo-nonanic acid methyl ester

IR (KBr): 2933.2, 2858.0, 2721.1, 1743.3, 1724.0,
1538.6, 1245.8, 1199.5, 1172.5 cm^{-1}

NMR (CDCl_3 , δ): 1.24 (6H, s), 1.3-1.7 (4H, m), 2.18 (2H,
t, $J=7.3\text{Hz}$), 2.29 (2H, t, $J=7.3\text{Hz}$), 3.58 (3H, s),
11.97 (1H, s)

Preparation 282

A solution of N-t-butoxycarbonyl-L-glutamic acid α -t-butyl ester (600 mg) and 4-piperidone hydrochloride monohydrate (455.6 mg) in dichloromethane (6 ml) - DMF (6 ml), was treated with 1-hydroxybenzotriazole (294 mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (460.5 mg) and stirred 15 hours at room temperature. The reaction was diluted with ethyl acetate and washed with water, dried over magnesium sulfate, evaporated, and the residue was purified by silica gel column chromatography (EtOAc elution) to give 4-(4-piperidon-1-yl)carbonyl-2-tert-butoxycarbonylamino-butanoic acid tert-butyl ester (450 mg) as a white solid.

IR (KBr): 3381, 2931, 2883, 1707, 1631.5, 1510, 1448,
1367, 1321 cm^{-1}

NMR (CDCl_3 , δ): 1.43 (9H, s), 1.48 (9H, s), 1.85-2.10
(1H, m), 2.15-2.4 (1H, m), 2.4-2.6 (6H, m), 3.6-4.1
(4H, m), 4.1-4.3 (1H, m), 5.19 (1H, br d, $J=8.4\text{Hz}$)

The following compound was obtained according to a similar manner to that of Preparation 282.

5 Preparation 283

1-(1-tert-Butoxycarbonylazetidin-3-yl)carbonyl-4-piperidone

IR (KBr): 2979.5, 2891, 1712.5, 1691.3, 1649 cm^{-1}

NMR (CDCl_3 , δ): 1.44 (9H, s), 2.44-2.53 (4H, m),

10 3.54-3.61 (3H, m), 3.89-3.95 (2H, m), 4.06-4.22 (4H, m)

MASS (m/z): 305.2 ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4 \cdot 0.6\text{H}_2\text{O}$:

C 57.36, H 7.98, N 9.56

15 Found: C 57.29, H 7.65, N 9.58

Preparation 284

To a solution of 1,3-dioxy-5-hydroxymethyl-4-methyl-2-oxo-4-cyclopentene (2 g) and N,N'-disuccinimidyl carbonate
20 (4.33 g) in dimethylformamide (10 ml) was added pyridine (1.37 ml) and stirred at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken and dried over magnesium sulfate.

The magnesium sulfate was filtered off, and the filtrate was
25 evaporated under reduced pressure to give (1,3-dioxy-2-oxo-4-cyclopenten-5-yl)methoxycarbonyloxysuccinimido (2.477 g).

IR (KBr): 1808.8, 1785.8, 1741.4, 1733.7, 1259.3, 1228.4, 1209.1 cm^{-1}

NMR (CDCl_3 , δ): 2.20 (3H, s), 2.86 (4H, s), 5.06 (2H, s)

30 ESI-MASS (m/z): 294.1 ($\text{M}^+ + \text{Na} + 1$)

Preparation 285

To a solution of 1-methyl-4-piperidone (1.0 g) in N,N-dimethylformamide (10 ml) was added 2-iodoethanol (0.70
35 ml - 1.5 g) and stirred overnight at ambient temperature.

The reaction mixture was evaporated under reduced pressure and washed by ethyl acetate to afford 1-(2-hydroxyethyl)-1-methyl-4-oxopiperidinium iodide (0.94 g).

MASS (m/z): 158 ($M^+ - I^-$)

5

Preparation 286

To a solution of 1-methyl-4-piperidone (1.0 g) in dichloromethane (5 ml) was slowly added iodomethane (1 ml) at 0°C and stirred for 30 minutes at ambient temperature. To the reaction mixture was added isopropyl ether (10 ml), and the resulting precipitate was collected by filtration to give 1,1-dimethyl-4-oxopiperidinium iodide (1.416 g).

NMR (DMSO- d_6 , δ): 1.87 (2H, t, $J=5.4\text{Hz}$), 2.71 (2H, t, $J=6.4\text{Hz}$), 3.09 (3H, s), 3.27 (3H, s), 3.30-3.40 (2H, m), 3.75 (2H, t, $J=6.6\text{Hz}$)

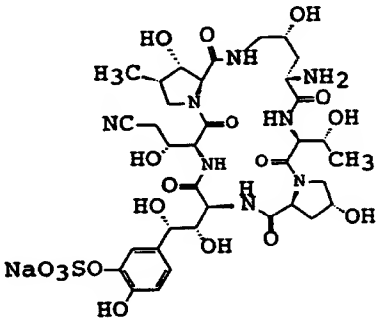
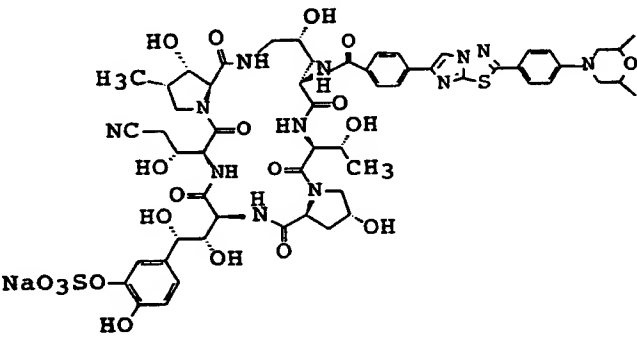
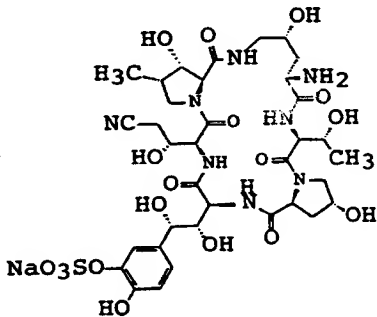
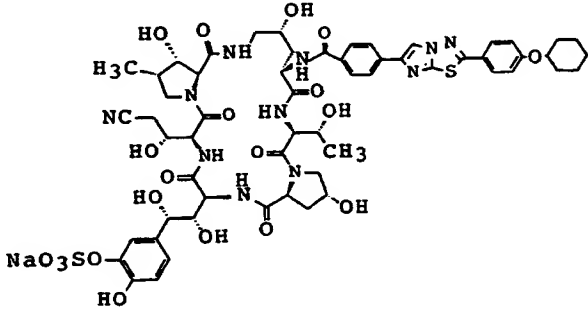
15

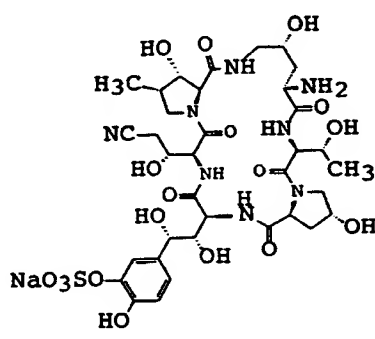
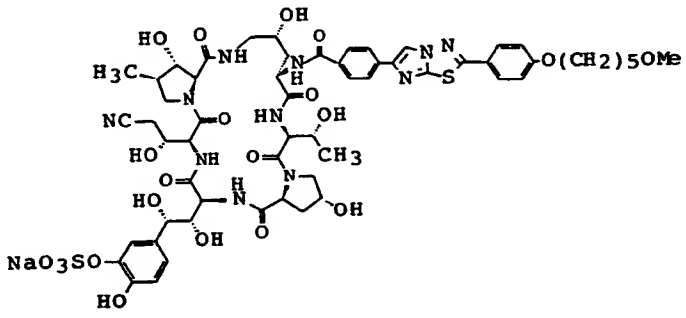
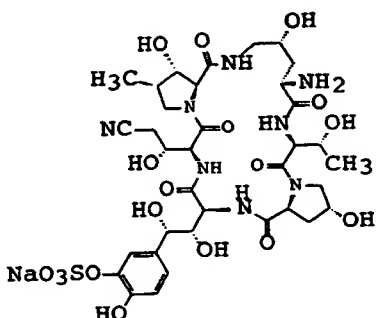
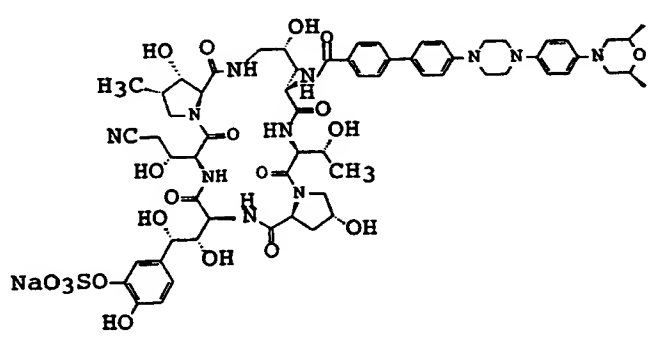
The Starting Compounds (287) to (290) used and the Object Compounds (287) to (290) obtained in the following Preparations 287 to 290 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

25

to be continued on the next page

30

Preparation No.	Formula
287	
	
288	
	

Preparation No.	Formula
289	
	
290	
	

The following compounds [Preparations 287 to 290] were obtained according to a similar manner to that of Preparation 10.

5

Preparation 287MASS (m/z): 1317.3 ($M^+ - Na$)Preparation 288

10

MASS (m/z): 1302.3 ($M^+ - Na$)Preparation 289MASS (m/z): 1320.3 ($M^+ - Na$)

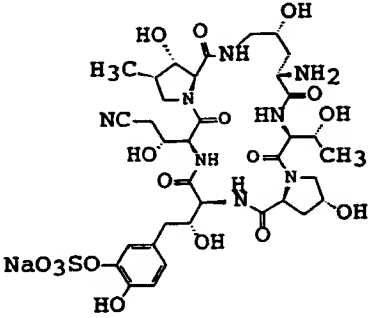
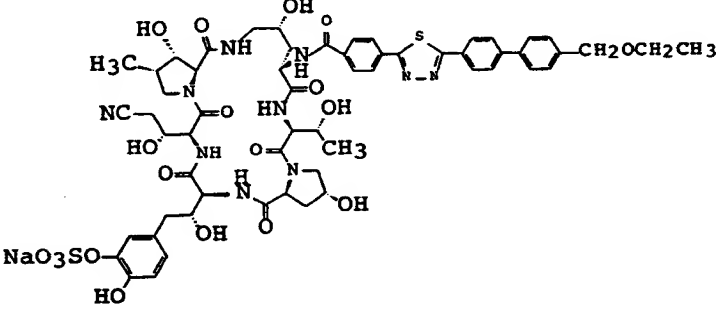
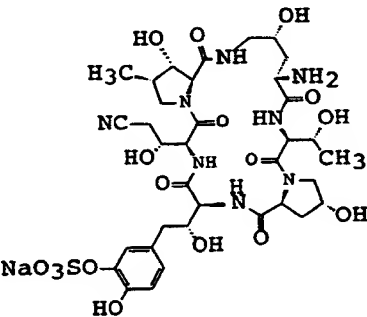
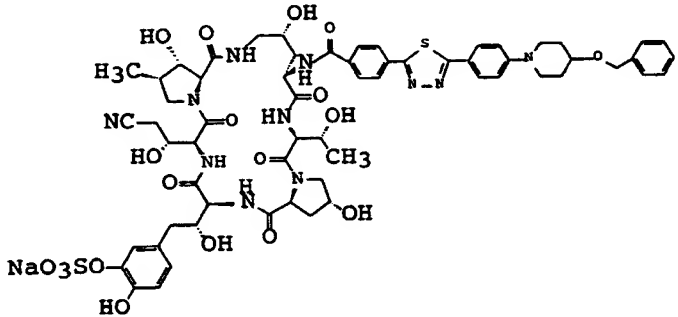
15

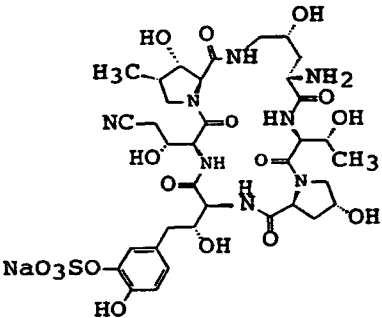
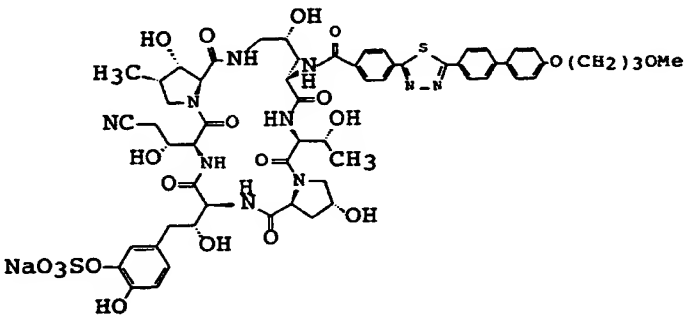
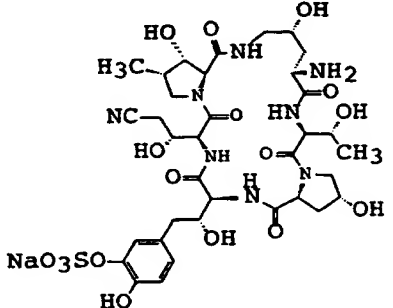
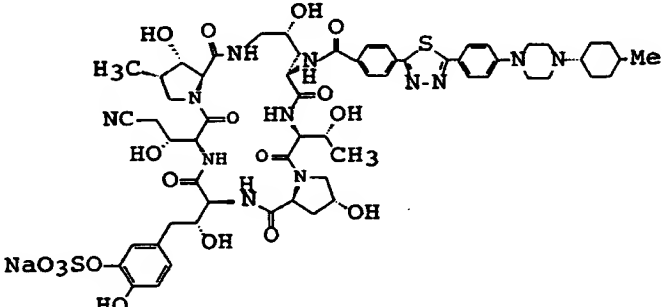
Preparation 290

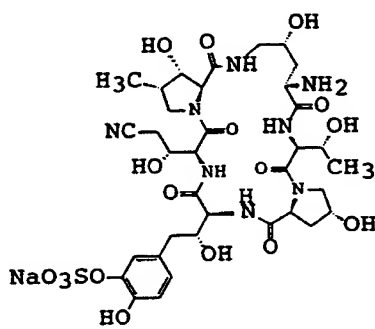
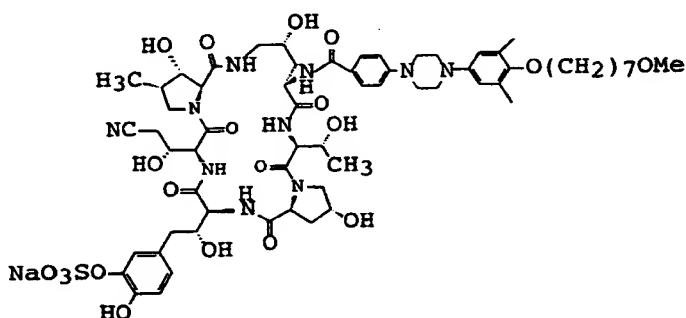
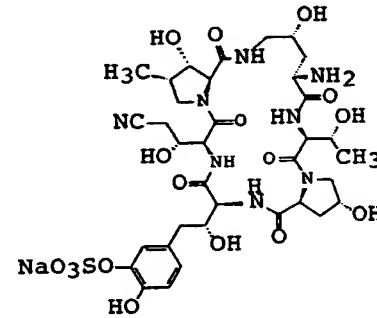
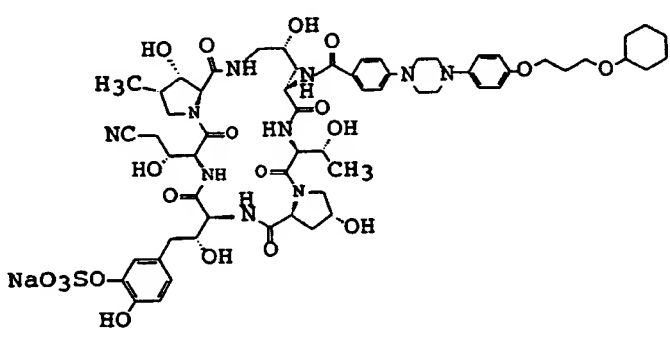
The object compound was used directly in the next reaction without purification.

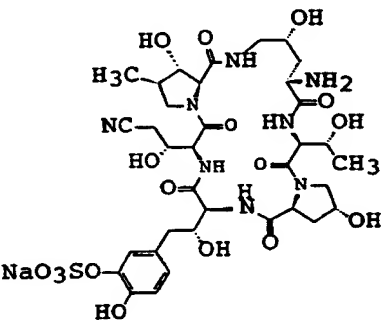
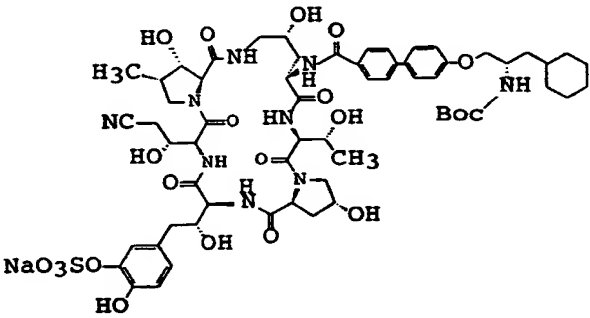
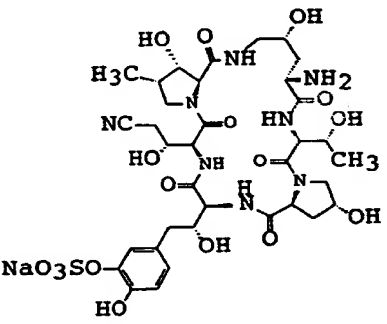
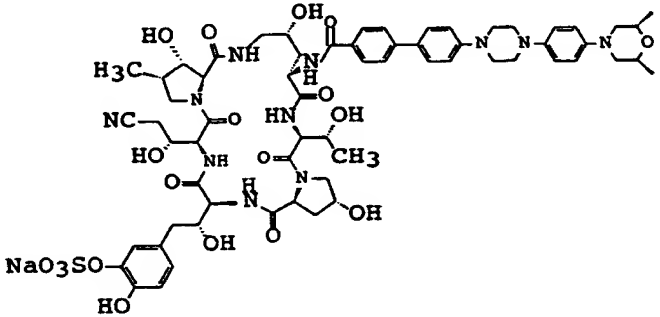
20

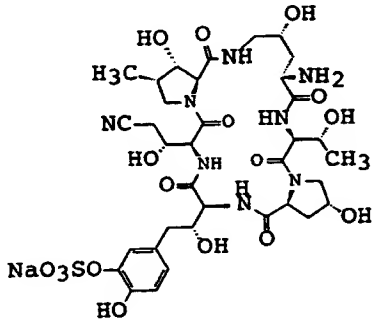
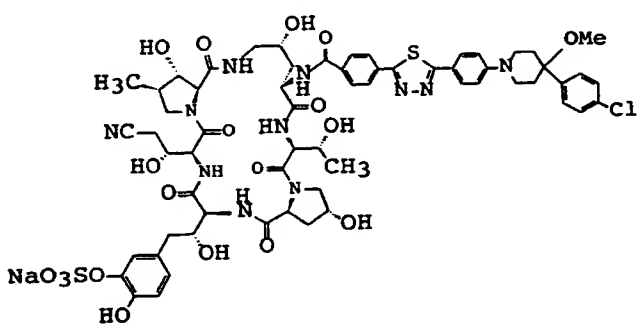
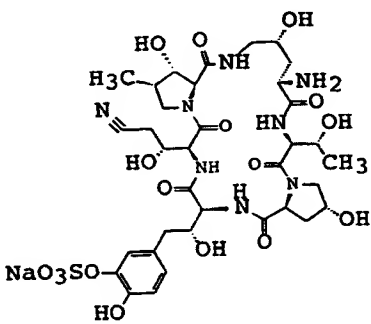
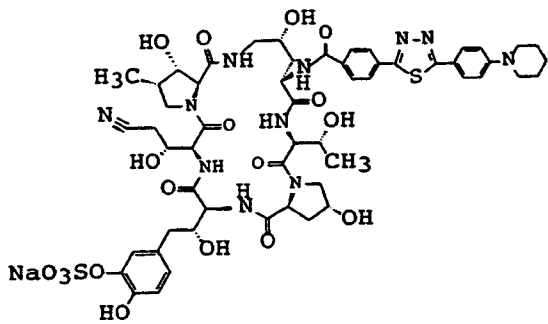
The Starting Compounds (291) to (338) used and the Object Compounds (291) to (338) obtained in the following Preparation 291 to 338 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

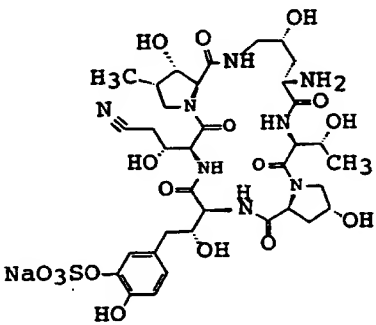
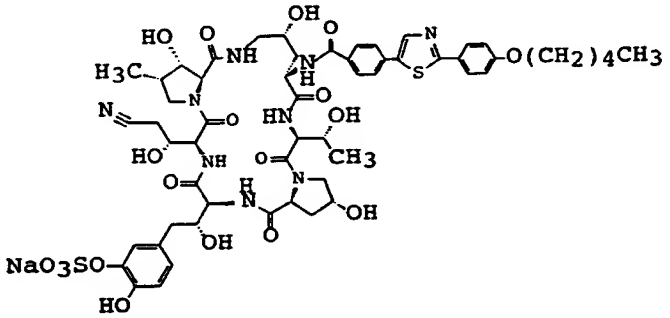
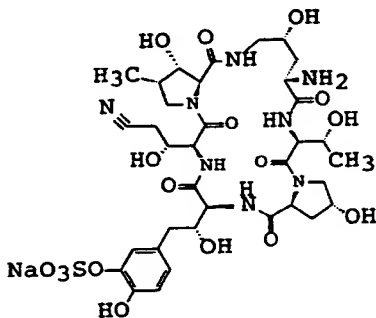
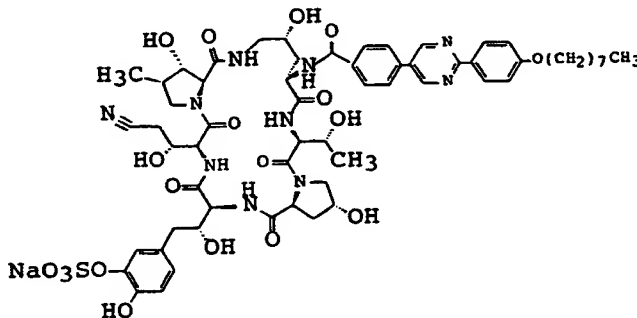
Preparation No.	Formula
291	
	
292	
	

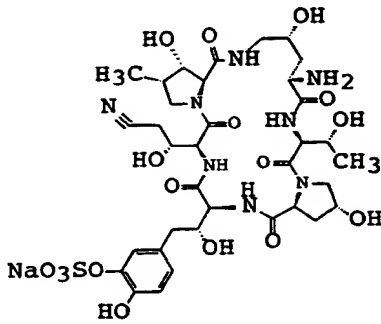
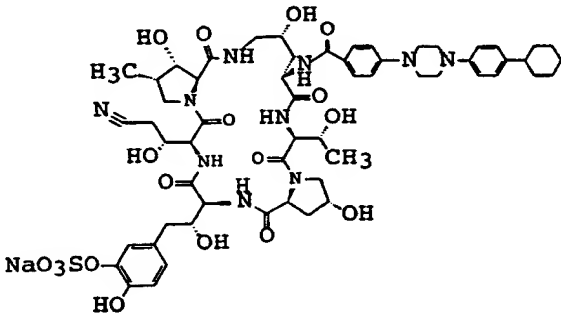
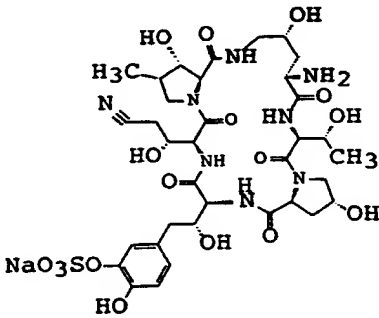
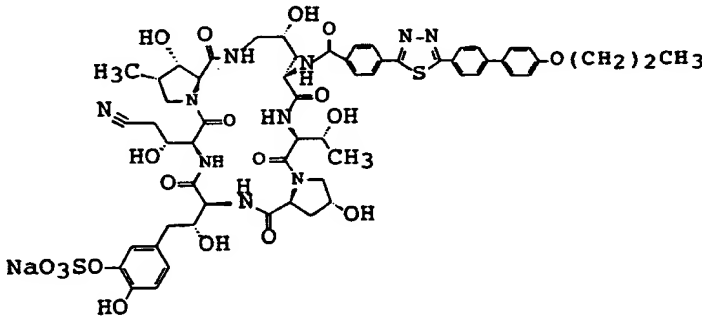
Preparation No.	Formula
293	 <p>Chemical structure of compound 293, a complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring.</p>
	 <p>Chemical structure of compound 293, showing a complex molecule with a central core, multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure also includes a long alkoxy chain (O(CH₂)₃OMe) and a thiazine ring system.</p>
294	 <p>Chemical structure of compound 294, a complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring.</p>
	 <p>Chemical structure of compound 294, showing a complex molecule with a central core, multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure also includes a long alkoxy chain (O(CH₂)₃OMe) and a thiazine ring system.</p>

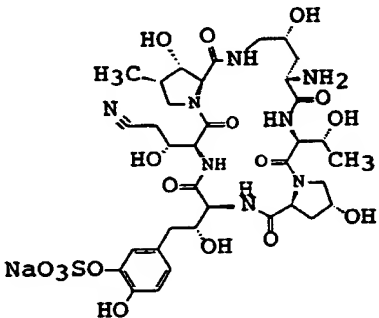
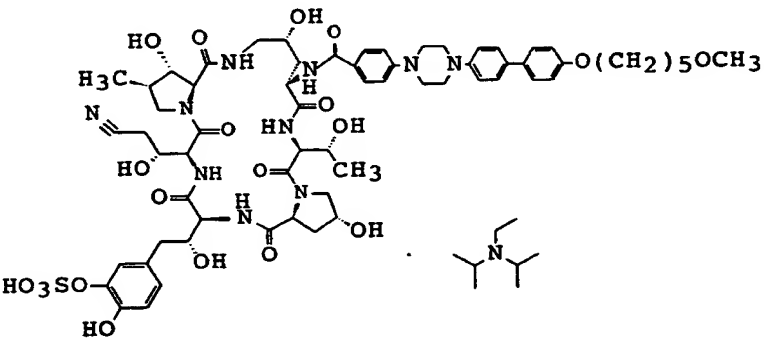
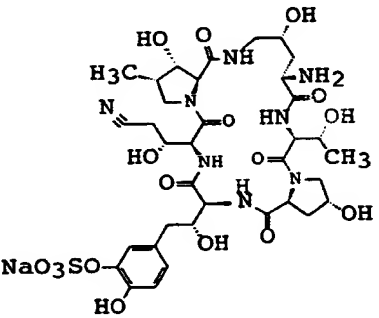
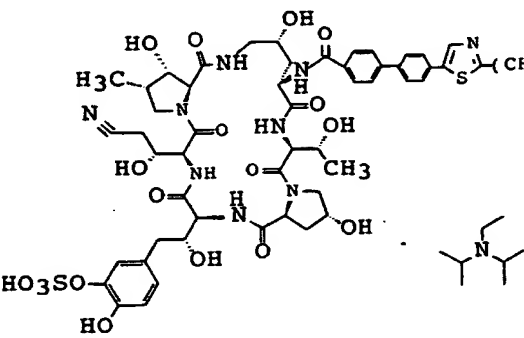
Preparation No.	Formula
295	
	
296	
	

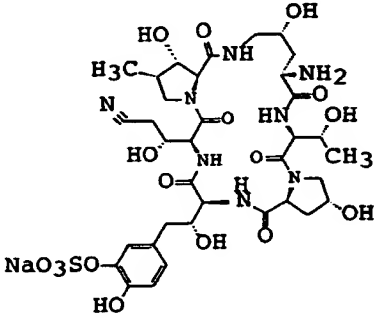
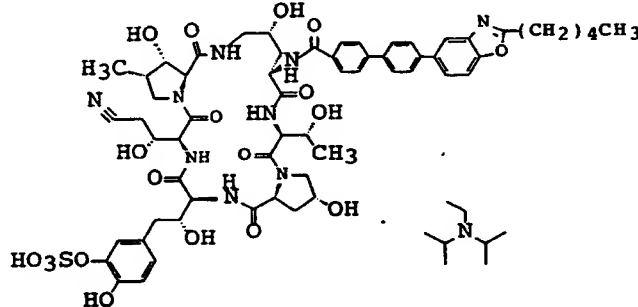
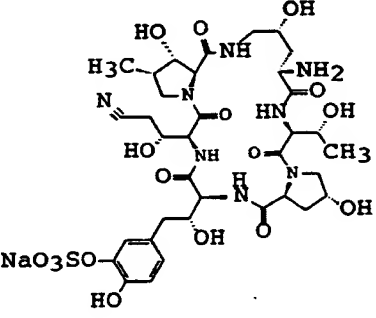
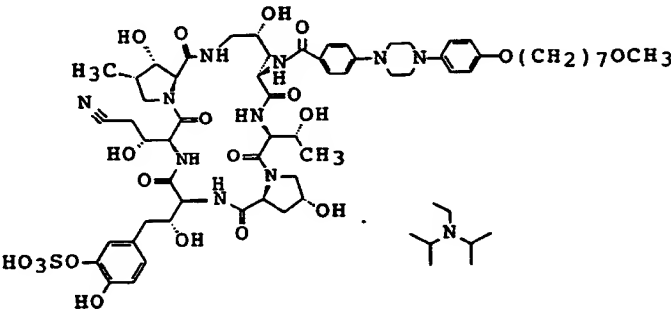
Preparation No.	Formula
297	
	
298	
	

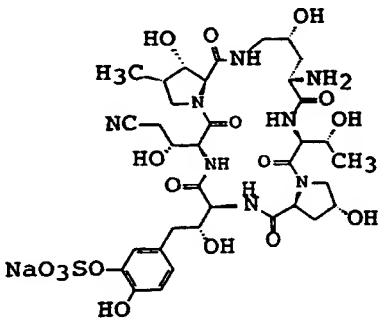
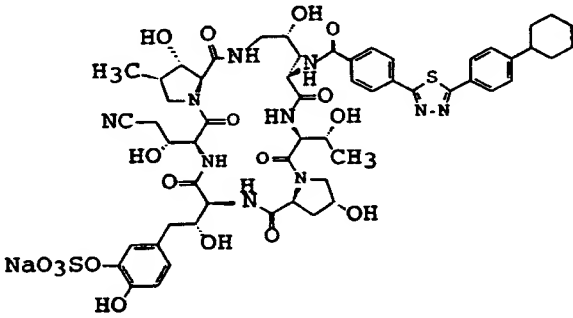
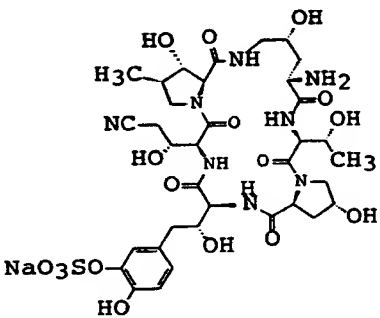
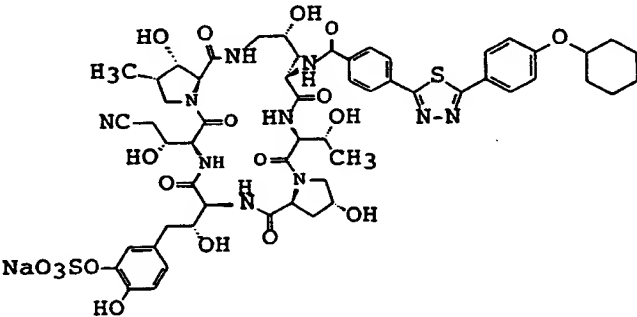
Preparation No.	Formula
299	 <p>Chemical structure of compound 299: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO). The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, and a pyridine ring with a hydroxyl group.</p>
	 <p>Chemical structure of compound 299: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO). The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, and a pyridine ring with a hydroxyl group. It also features a thiazole ring and a methoxy group (OMe).</p>
300	 <p>Chemical structure of compound 300: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO). The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, and a pyridine ring with a hydroxyl group.</p>
	 <p>Chemical structure of compound 300: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO). The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, and a pyridine ring with a hydroxyl group. It also features a thiazole ring and a methoxy group (OMe).</p>

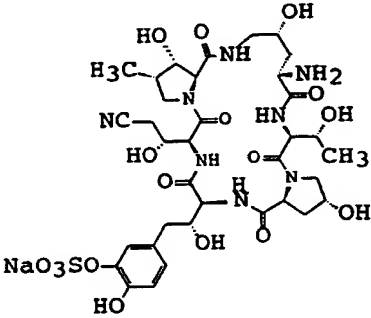
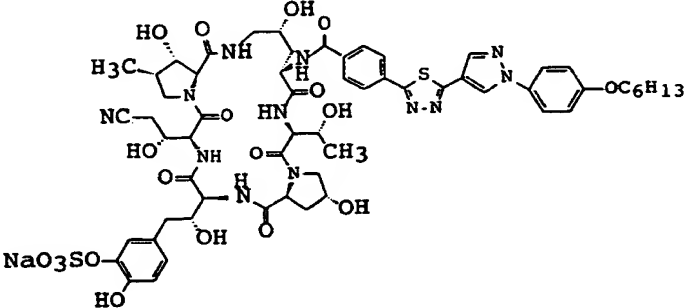
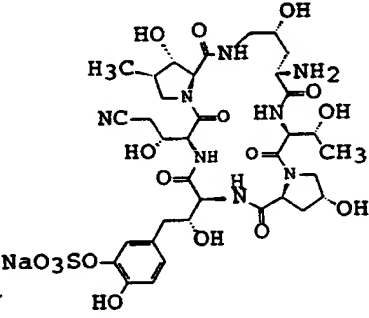
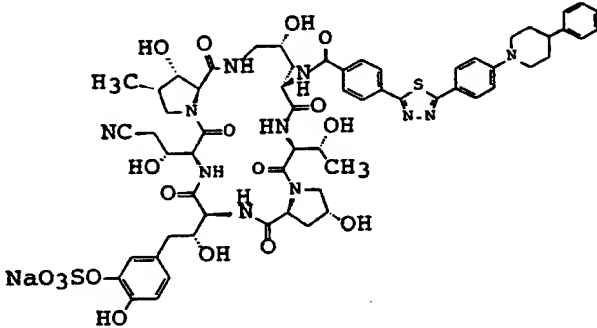
Preparation No.	Formula
301	 <p>Chemical structure of Preparation 301: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO-) attached to a phenyl ring. The structure includes several amide and ester linkages, and a methyl group (H₃C).</p>
	 <p>Chemical structure of Preparation 301 (continued): The structure continues from the previous one, showing a long chain with a thioether linkage (S) and a terminal group consisting of a phenyl ring and a long alkyl chain (O(CH₂)₄CH₃).</p>
302	 <p>Chemical structure of Preparation 302: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO-) attached to a phenyl ring. The structure includes several amide and ester linkages, and a methyl group (H₃C).</p>
	 <p>Chemical structure of Preparation 302 (continued): The structure continues from the previous one, showing a long chain with a thioether linkage (S) and a terminal group consisting of a phenyl ring and a long alkyl chain (O(CH₂)₇CH₃).</p>

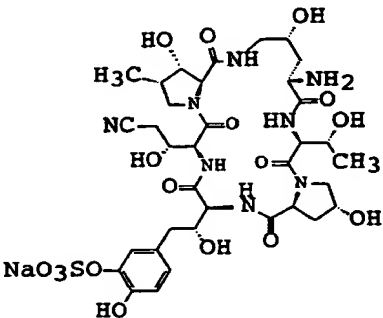
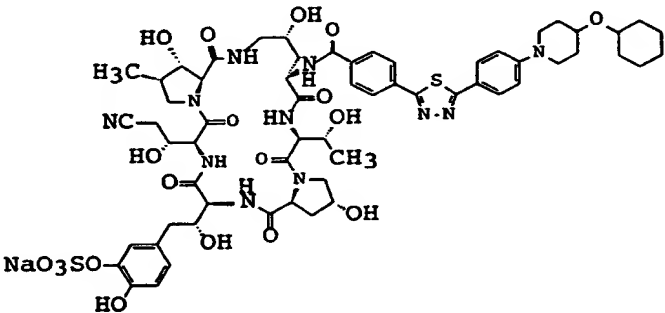
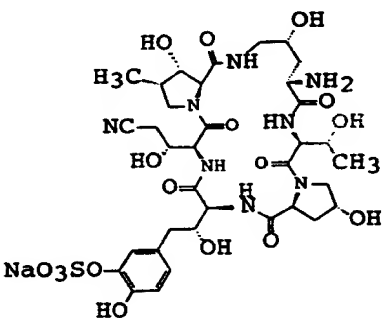
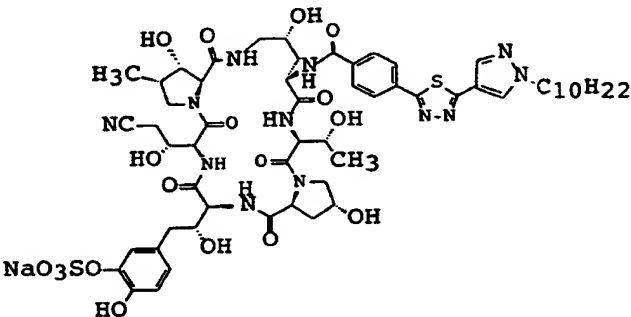
Preparation No.	Formula
303	 <p>Chemical structure of Preparation 303: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure includes several amide and ester linkages, and a cyclohexyl group is present on the right side.</p>
	 <p>Chemical structure of Preparation 303 (continued): This structure shows a variation of the core molecule, featuring a different side chain with a cyclohexyl group and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring.</p>
304	 <p>Chemical structure of Preparation 304: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure includes several amide and ester linkages, and a cyclohexyl group is present on the right side.</p>
	 <p>Chemical structure of Preparation 304 (continued): This structure shows a variation of the core molecule, featuring a different side chain with a cyclohexyl group and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring.</p>

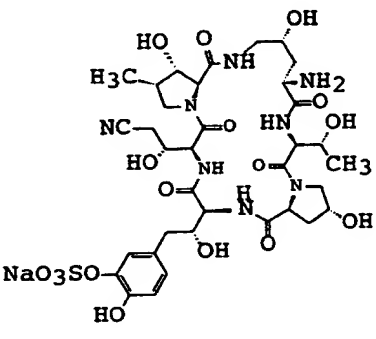
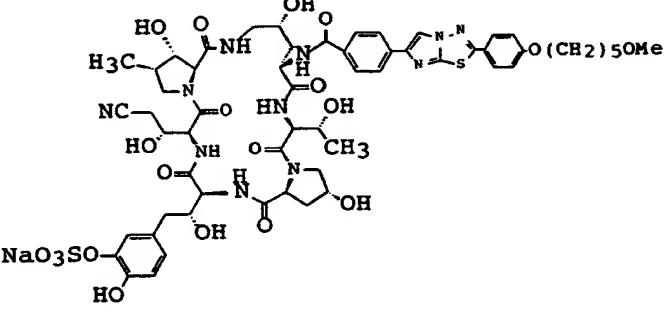
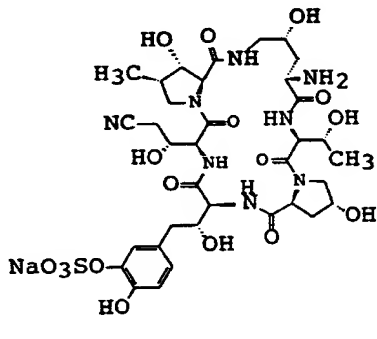
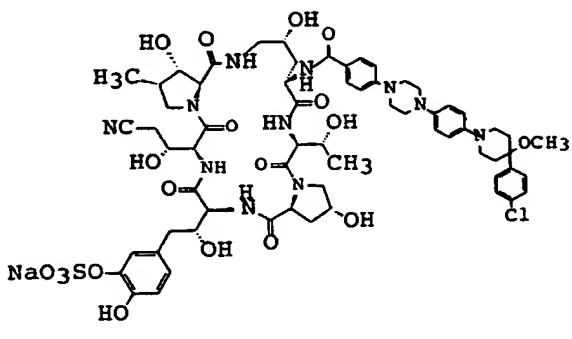
Preparation No.	Formula
305	
	
306	
	

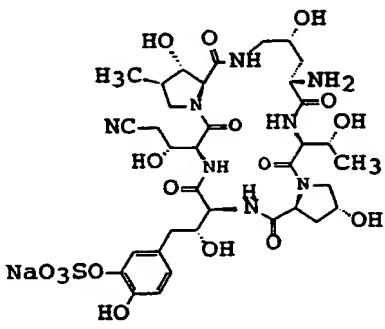
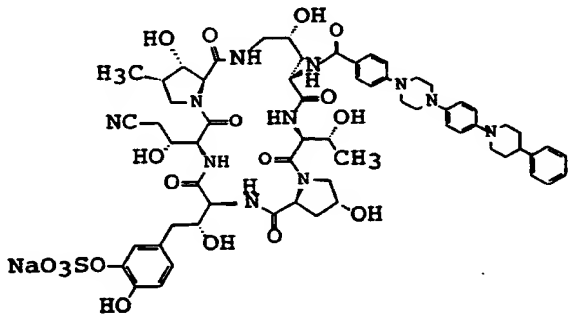
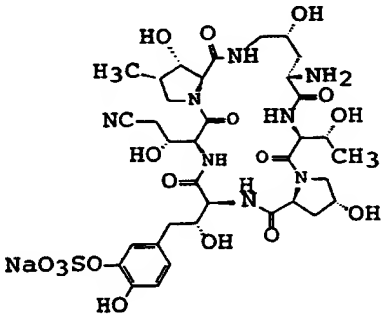
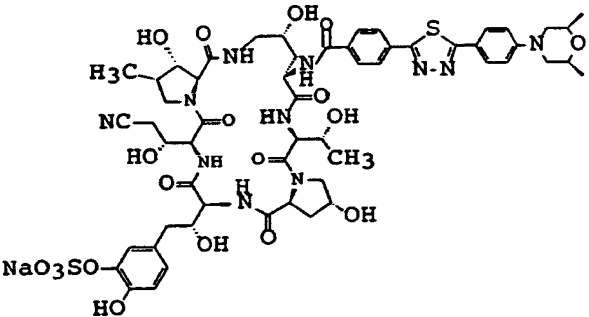
Preparation No.	Formula
307	 <p>Chemical structure of Preparation 307, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 307, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sulfonate group (HO₃SO) attached to a phenyl ring. It also includes a long chain with a terminal group (CH₂)₄CH₃ and a dimethylamino group.</p>
308	 <p>Chemical structure of Preparation 308, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 308, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sulfonate group (HO₃SO) attached to a phenyl ring. It also includes a long chain with a terminal group (CH₂)₇OCH₃ and a dimethylamino group.</p>

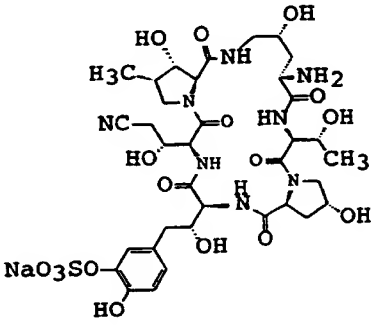
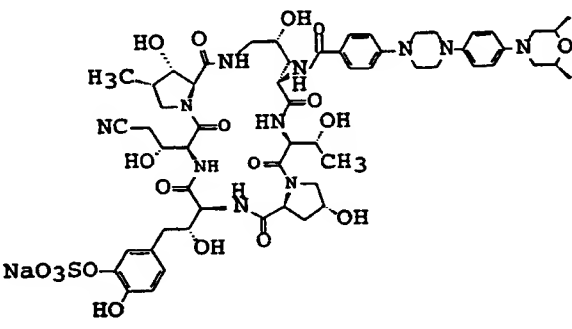
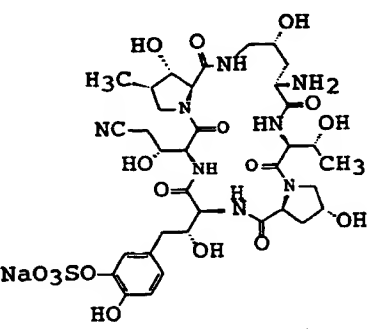
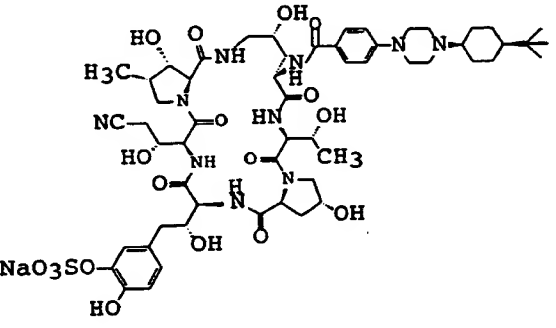
Preparation No.	Formula
309	 <p>Chemical structure of Preparation 309, top formula. It features a central bicyclic core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO-) attached to a phenyl ring. The structure is complex, showing various amide and ester linkages.</p>
	 <p>Chemical structure of Preparation 309, bottom formula. It is similar to the top formula but includes an additional phenyl ring substituted with a sulfonamide group (SO₂NH-) and a cyclohexyl group.</p>
310	 <p>Chemical structure of Preparation 310, top formula. It is similar to the top formula of Preparation 309 but lacks the additional phenyl ring and sulfonamide group.</p>
	 <p>Chemical structure of Preparation 310, bottom formula. It is similar to the bottom formula of Preparation 309 but lacks the additional phenyl ring and sulfonamide group.</p>

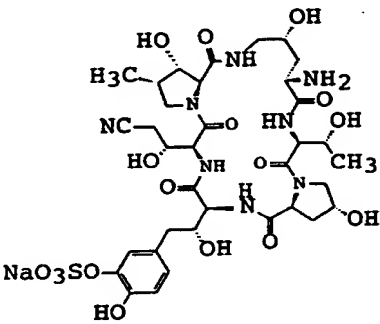
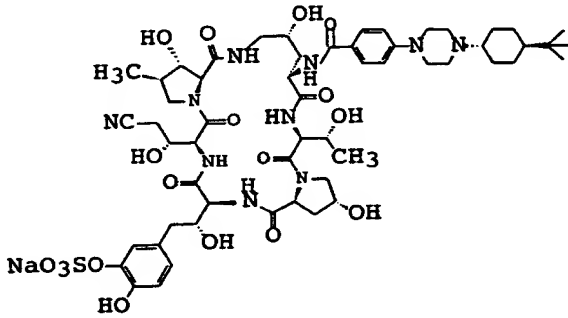
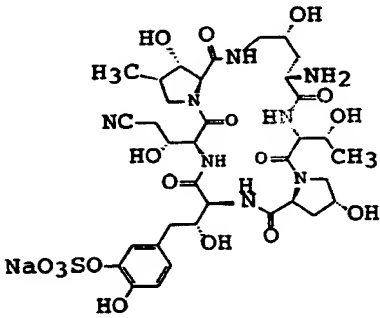
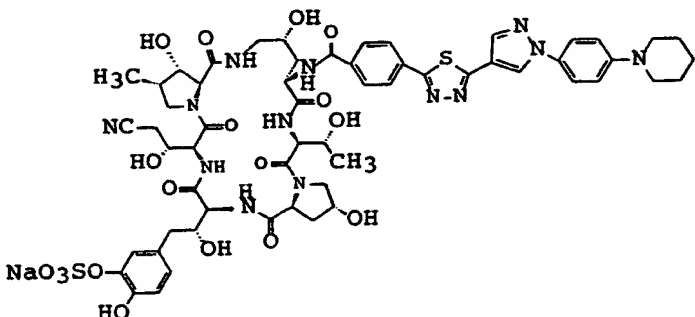
Preparation No.	Formula
311	 <p>Chemical structure of Preparation 311, top formula. It features a central bicyclic core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 311, bottom formula. It features a central bicyclic core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring. It also includes a long alkoxy chain (OC₆H₁₃) and a thioether linkage.</p>
312	 <p>Chemical structure of Preparation 312, top formula. It features a central bicyclic core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 312, bottom formula. It features a central bicyclic core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring. It also includes a thioether linkage and a phenyl group.</p>

Preparation No.	Formula
313	
	
314	
	

Preparation No.	Formula
315	
	
316	
	

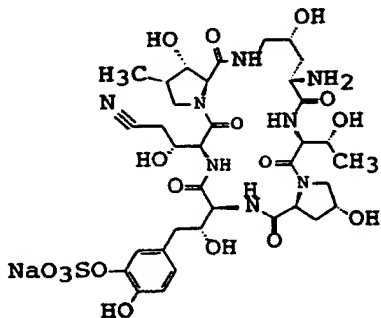
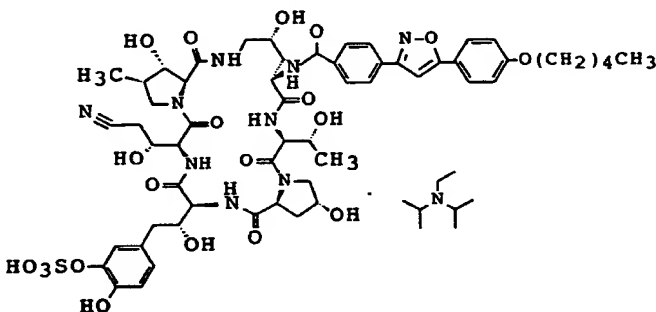
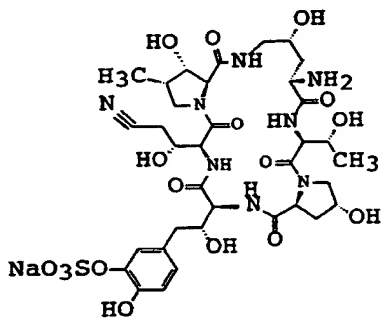
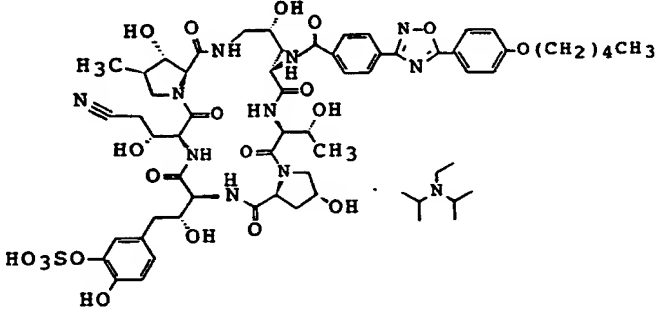
Preparation No.	Formula
317	
	
318	
	

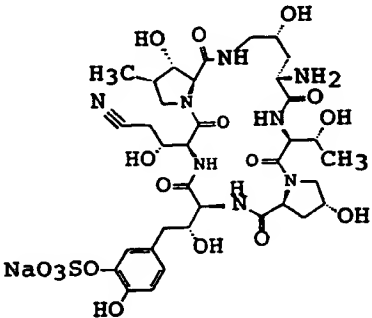
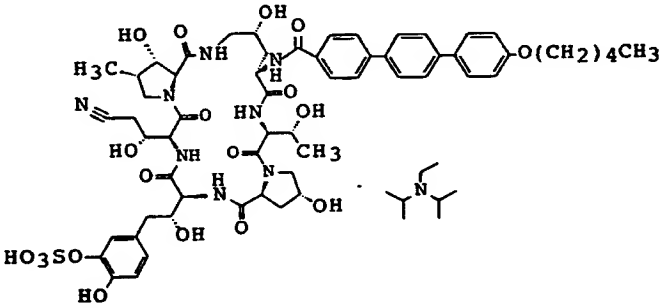
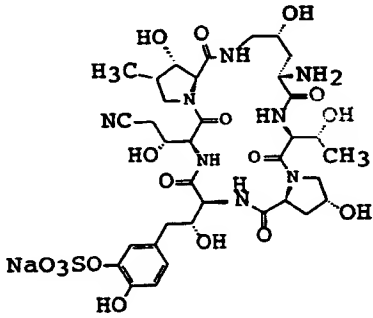
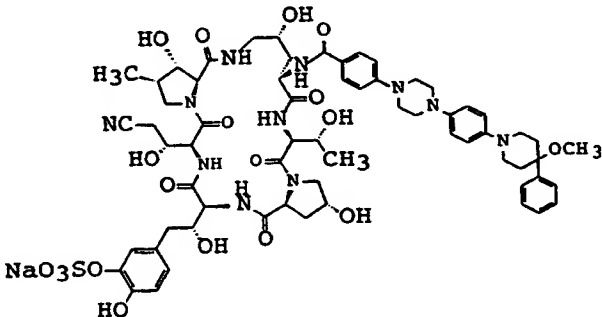
Preparation No.	Formula
319	
	
320	
	

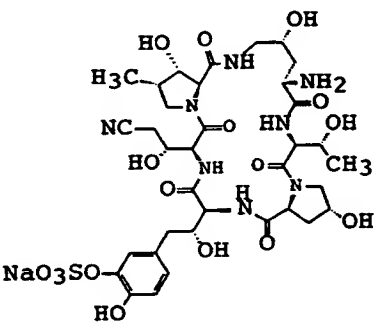
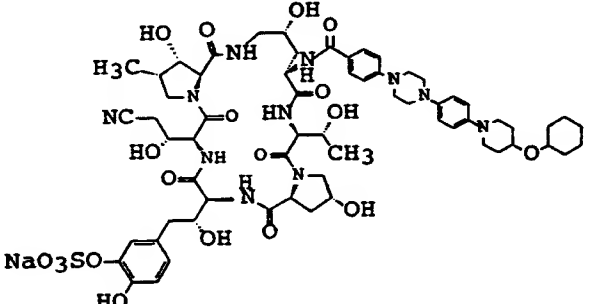
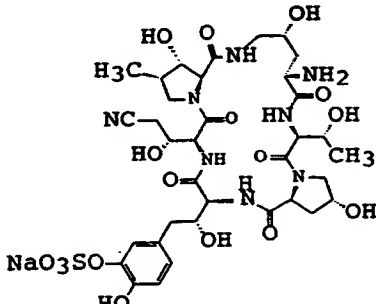
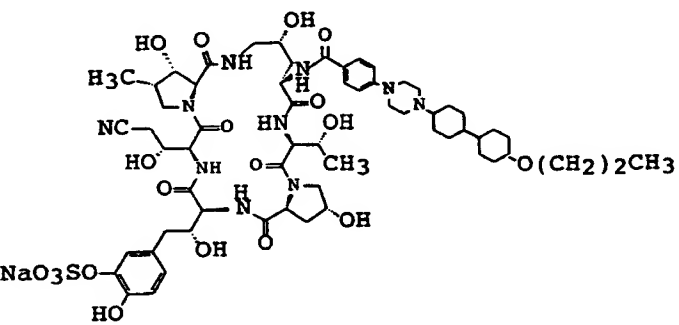
Preparation No.	Formula
321	 <p>Chemical structure of Preparation 321, top formula. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 321, bottom formula. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring. The structure also includes a complex side chain with a piperazine ring and a cyclohexyl group.</p>
322	 <p>Chemical structure of Preparation 322, top formula. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 322, bottom formula. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group attached to a phenyl ring. The structure also includes a complex side chain with a piperazine ring and a cyclohexyl group.</p>

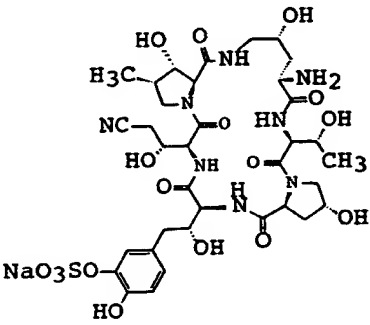
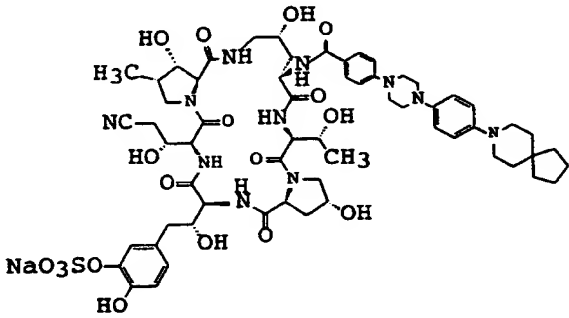
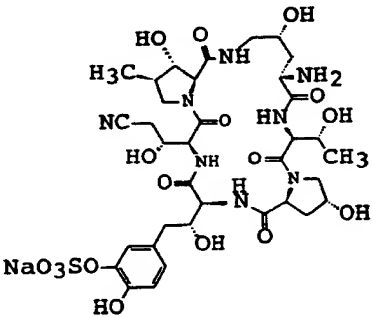
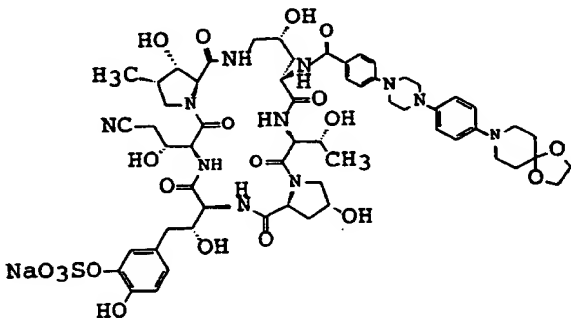
Preparation No.	Formula
323	
324	

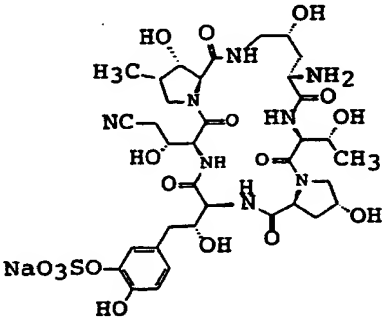
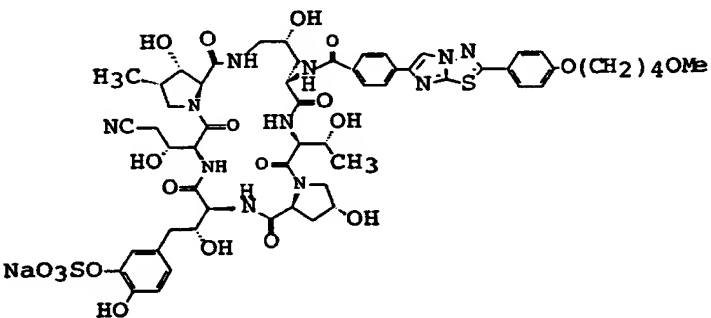
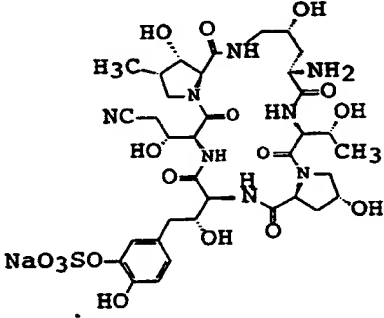
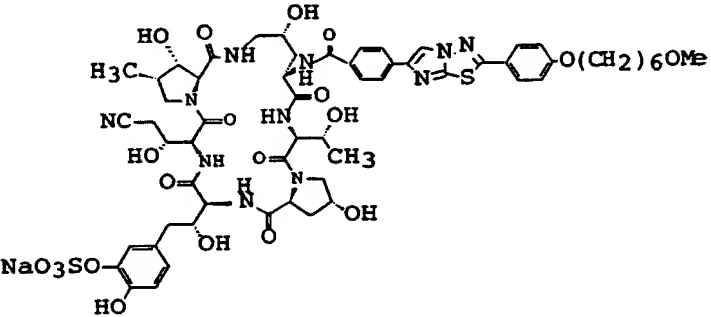
Preparation No.	Formula
325	
326	

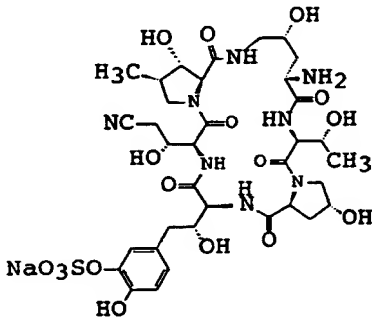
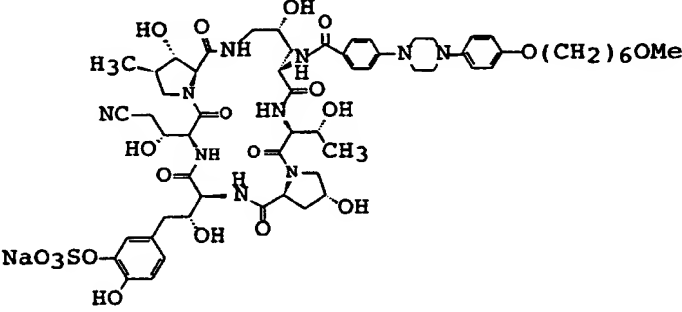
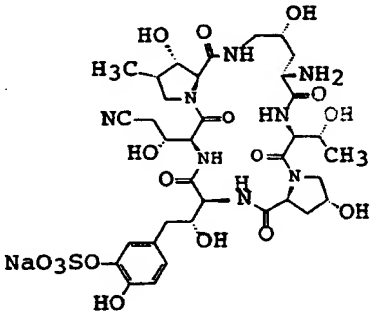
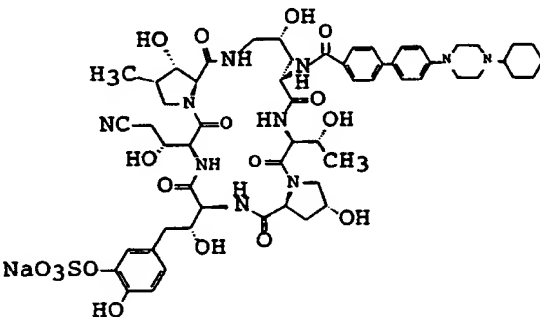
Preparation No.	Formula
327	
	
328	
	

Preparation No.	Formula
329	
	
330	
	

Preparation No.	Formula
331	 <p>Chemical structure of Preparation 331, top part. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure is complex, involving several amide and ester linkages.</p>
	 <p>Chemical structure of Preparation 331, bottom part. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure is complex, involving several amide and ester linkages, and includes a long chain with a terminal group.</p>
332	 <p>Chemical structure of Preparation 332, top part. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure is complex, involving several amide and ester linkages.</p>
	 <p>Chemical structure of Preparation 332, bottom part. It features a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure is complex, involving several amide and ester linkages, and includes a long chain with a terminal group.</p>

Preparation No.	Formula
333	
	
334	
	

Preparation No.	Formula
335	
	
336	
	

Preparation No.	Formula
337	
	
338	
	

The following compounds [Preparations 291 to 338] were obtained according to a similar manner to that of Preparation 10.

5 Preparation 291

MASS (m/z): 1283.3 ($M^+ - Na$)

Preparation 292

MASS (m/z): 1338.3 ($M^+ - Na$)

10

Preparation 293

MASS (m/z): 1313.2 ($M^+ - Na$)

Preparation 294

15 MASS (m/z): 1329.3 ($M^+ - Na$)

Preparation 295

MASS (m/z): 1321.5 ($M^+ - Na$)

20 Preparation 296

The object compound was used directly in the next reaction without purification.

Preparation 297

25 MASS (m/z): 1320.4 ($M^+ - Na$)

Preparation 298

The object compound was used directly in the next reaction without purification.

30

Preparation 299

IR (KBr): 1605, 1444 cm^{-1}

MASS (m/z): 1372 ($M - 2H$)

K

Preparation 300

MASS (m/z): 1232.2 (M^+ -Na)

Preparation 301

- 5 The object compound was used directly in the next reaction without purification.

Preparation 302

- 10 The object compound was used directly in the next reaction without purification.

Preparation 303

- 15 The object compound was used directly in the next reaction without purification.

Preparation 304

 The object compound was used directly in the next reaction without purification.

- 20 Preparation 305

 The object compound was used directly in the next reaction without purification.

Preparation 306

- 25 The object compound was used directly in the next reaction without purification.

Preparation 307

- 30 The object compound was used directly in the next reaction without purification.

Preparation 308

- 35 The object compound was used directly in the next reaction without purification.

Preparation 309

The object compound was used directly in the next reaction without purification.

5 Preparation 310

The object compound was used directly in the next reaction without purification.

Preparation 311

10 MASS (m/z): 1361 ($M^+ + 23$)

Preparation 312

MASS (m/z): 1308 ($M^+ - 23$)

15 Preparation 313

The object compound was used directly in the next reaction without purification.

Preparation 314

20 The object compound was used directly in the next reaction without purification.

Preparation 315

25 MASS (m/z): 1304.3 ($M^+ - Na$)

Preparation 316

IR (KBr): 3345.9, 1633.4, 1511.9, 1232.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.8Hz$), 1.08 (3H, d, $J=6.1Hz$), 1.23-1.26 (2H, m), 2.80-5.21 (51H, m),
30 6.66-8.72 (20H, m)

MASS (m/z): 1372.3 ($M^+ - Na$)

Preparation 317

IR (KBr): 3336.2, 1631.5, 1510.0, 1230.4 cm^{-1}

35 NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=7.1Hz$), 1.08 (3H, d,

J=5.8Hz), 1.24-5.21 (50H, m), 6.68-8.72 (22H, m)
MASS (m/z): 1308.4 (M^+ -Na)

Preparation 318

5 MASS (m/z): 1262(M^+ -23)

Preparation 319

MASS (m/z): 1262(M^+ -23)

10 Preparation 320

The object compound was used directly in the next reaction without purification.

Preparation 321

15 The object compound was used directly in the next reaction without purification.

Preparation 322

20 The object compound was used directly in the next reaction without purification.

Preparation 323

25 The object compound was used directly in the next reaction without purification.

Preparation 324

The object compound was used directly in the next reaction without purification.

30 Preparation 325

The object compound was used directly in the next reaction without purification.

Preparation 326

35 The object compound was used directly in the next

reaction without purification.

Preparation 327

5 The object compound was used directly in the next
reaction without purification.

Preparation 328

10 The object compound was used directly in the next
reaction without purification.

Preparation 329

The object compound was used directly in the next
reaction without purification.

15 Preparation 330

IR (KBr): 3351.7, 2256.3, 1633.4, 1232.3, 1116.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d,
 $J=5.9\text{Hz}$), 1.80-5.20 (52H, m), 5.91-5.94 (1H, m),
6.68-8.72 (21H, m)

20 MASS (m/z): 1338.4 ($\text{M}^+ - \text{Na}$)

Preparation 331

IR (KBr): 2256.3, 1633.4, 1510.0, 1085.7 cm^{-1}

NMR (DMSO- d_6 , δ): 0.94-5.93 (68H, m), 6.69-8.72 (16H, m)

25 MASS (m/z): 1330.5 ($\text{M}^+ - \text{Na}$)

Preparation 332

IR (KBr): 3351.7, 2256.3, 1666.2, 1633.4, 1230.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.81-5.20 (74H, m), 5.88-5.91 (1H, m),
30 6.68-8.72 (12H, m)

Preparation 333

IR (KBr): 2256.3, 1633.4, 1510.0, 1322.9, 1232.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d,
35 $J=5.6\text{Hz}$), 1.24-5.20 (57H, m), 5.89-5.93 (1H, m),

6.68-8.79 (16H, m)

MASS (m/z): 1286.3 (M^+ -Na)

Preparation 334

5 IR (KBr): 3349.7, 2256.3, 1633.4, 1232.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.5\text{Hz}$), 1.70-5.21 (53H, m), 5.90-5.93 (1H, m), 6.68-8.72 (16H, m)

MASS (m/z): 1336.3 (M^+ +Na)

10

Preparation 335

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.6-2.0 (8H, m), 2.2-2.5 (3H, m), 2.7 (1H, m), 2.9 (2H, m), 3.23 (3H, s), 3.34 (2H, m), 3.74 (2H, m), 3.6-4.6 (15H, m), 4.85 (3H, m), 5.03 (1H, d, $J=6.2\text{Hz}$), 5.10 (1H, m), 5.20 (2H, m), 5.88 (1H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=8.2\text{Hz}$), 6.98 (1H, s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.42 (1H, d, $J=8.3\text{Hz}$), 7.51 (1H, d, $J=9.3\text{Hz}$), 7.79 (1H, m), 7.90 (2H, d, $J=8.9\text{Hz}$), 7.97 (4H, s), 8.32 (1H, d, $J=7.7\text{Hz}$), 8.51 (1H, d, $J=7.5\text{Hz}$), 8.71 (1H, m), 8.84 (1H, s)

15

20

MASS (m/z): 1290.3 (M^+ +Na)

25 Preparation 336

MASS (m/z): 1318.3 (M^+ -Na)

Preparation 337

MASS (m/z): 1279.4 (M^+ -Na)

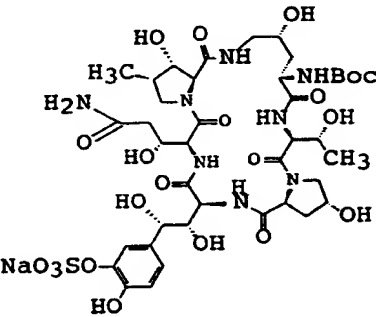
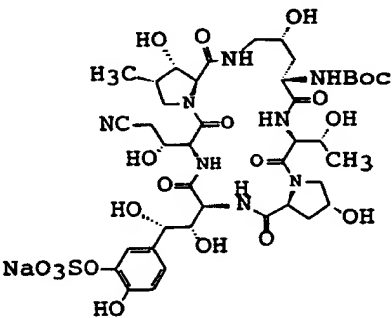
30

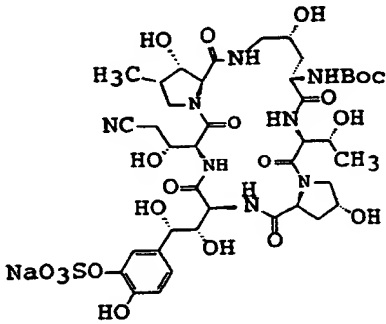
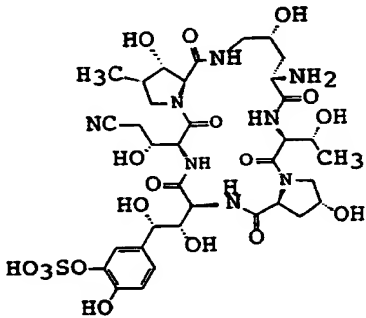
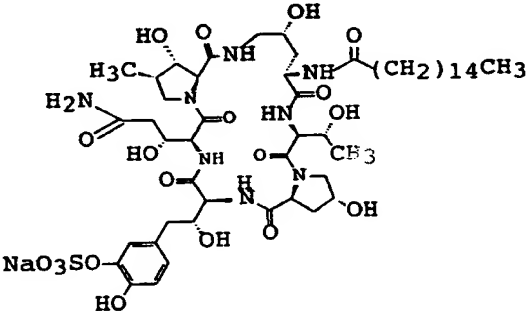
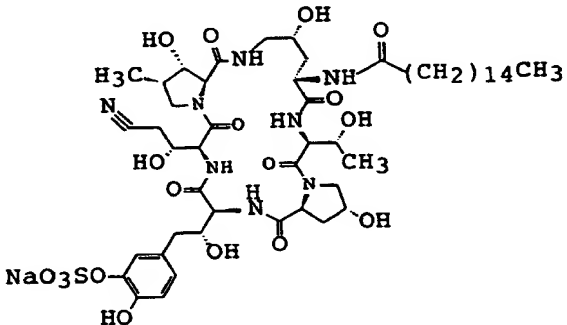
Preparation 338

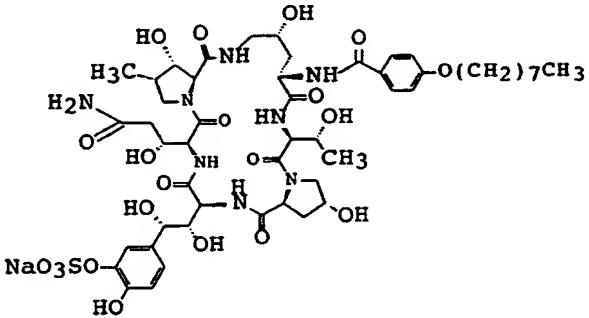
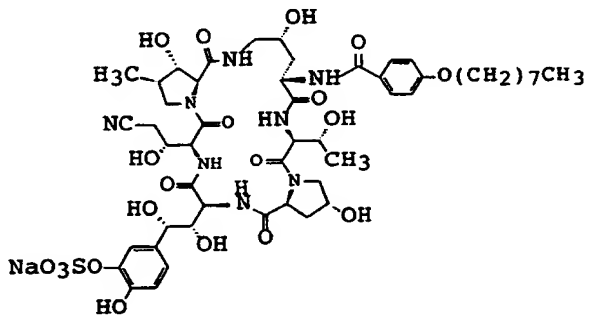
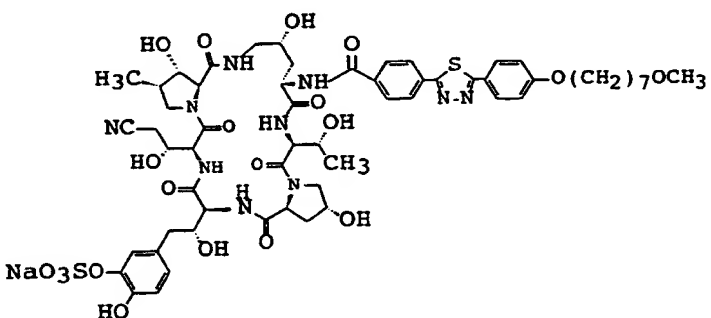
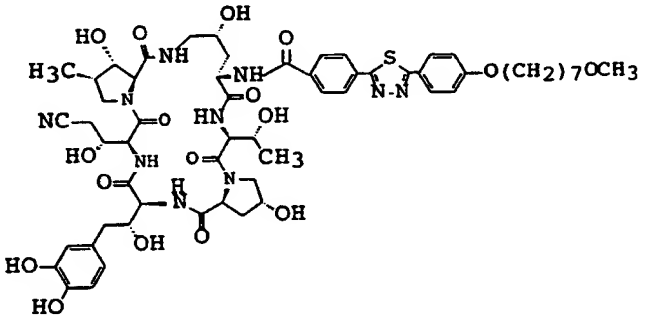
MASS (m/z): 1231.4 (M^+ -Na)

35

The Starting Compounds (339) to (343) used and the Object Compounds (339) to (343) obtained in the following Preparations 339 to 343 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

Preparation No.	Formula
339	
	

Preparation No.	Formula
340	
	
341	
	

Preparation No.	Formula
342	
	
343	
	

The following compound was obtained according to a similar manner to that of Preparation 2.

5

Preparation 339

IR (KBr): 1666, 1633, 1516, 1443, 1279, 1254 cm^{-1}

NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.94 (3H, d, $J=6.74\text{Hz}$), 1.09 (3H, d, $J=5.59\text{Hz}$), 1.36 (9H, s), 1.50-2.00 (3H, m),
10 2.10-2.40 (3H, m), 2.55-3.40 (5H, m), 3.55-4.50 (12H, m), 4.70-4.90 (2H, m), 6.73 (1H, d, $J=8.20\text{Hz}$), 6.82 (1H, d, $J=9.80\text{Hz}$), 7.06 (1H, s)

ESI MASS (m/z)(Positive): 1047.2 ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{40}\text{H}_{57}\text{N}_8\text{O}_{20}\text{SNa} \cdot 5\text{H}_2\text{O}$:

15 C 43.09, H 6.06, N 10.05

Found: C 43.05, H 6.09, N 9.98

HPLC (20% CH_3CN -pH 6.86 standard buffer solution;
YMC-ODS 150x4.6mm): LT 5.38 min.

20

The following compound was obtained according to a similar manner to that of Preparation 9.

Preparation 340

25 NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.94 (3H, d, $J=6.74\text{Hz}$), 1.14 (3H, d, $J=5.89\text{Hz}$), 1.30-1.55 (1H, m), 1.70-2.00 (1H, m), 2.05-2.45 (3H, m), 2.50-2.90 (3H, m), 3.05-3.35 (1H, m), 3.50-4.50 (16H, m), 4.65-4.95 (2H, m), 6.70-6.85 (2H, m), 7.09 (1H, d, $J=1.56\text{Hz}$)

ESI MASS (m/z)(Positive): 925.2 (M^+)

30 HPLC (20% CH_3CN -pH 6.86 standard buffer solution;
YMC-ODS 150x4.6mm): LT 2.01 min.

The following compounds [Preparation 341 to 342] were obtained according to a similar manner to that of Preparation
35 2.

Preparation 341

IR (KBr): 3354, 2925.5, 2854, 2256, 1631.5, 1535, 1516,
1448, 1267, 1246, 1084, 1047 cm^{-1}

5 MASS (m/z): 1123.5 ($\text{M}^+ - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{51}\text{H}_{79}\text{N}_8\text{O}_{18}\text{SNa} \cdot 7\text{H}_2\text{O}$:

C 48.10, H 7.36, N 8.80

Found: C 48.31, H 7.26, N 8.72

10 The following compound was obtained according to a similar manner to that of Preparation 2.

Preparation 342

IR (KBr): 2931, 1659, 1635, 1531, 1506, 1439, 1387,
15 1350 cm^{-1}

MASS (m/z): 1133.4 ($\text{M}^+ - \text{Na}$)

Preparation 343

20 To a solution of Starting Compound (343) (1 g) in trifluoroacetic acid (20 ml) was added 1N HCl aq. (4 ml) and stirred for 7 hours at ambient temperature. The reaction mixture was pulverized with water (90 ml). The precipitate was collected by filtration and dried under reduced pressure.

The powder was added to 36% acetonitrile aq. (190 ml) and
25 subjected to column chromatography on ODS (YMC-gel ODS-AM X S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 35% acetonitrile aq. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was
30 lyophilized to give Object Compound (343) (319 mg).

IR (KBr): 3344.0, 2254, 1658.5, 1635.3, 1444.4,
1257.4 cm^{-1}

ESI-MASS (m/z): 1213 ($\text{M}^+ - 1$)

Preparation 344

Dimethylformamide (485 /), p-pentyloxyacetophenone (30.3 kg) and dimethyl terephthalate (45.6 kg) were charged in 2000-liter reactor and stirred. To this mixture was added
5 potassium tert-butoxide (24.7 kg) in several portions and, after that, a reaction was carried out at the inner temperature of 20 to 25°C for 3.5 hours. After completion of the reaction, methanol (1210 /) was added to the reaction solution at 20 to 30°C and then 6N hydrochloric acid (49 /) at
10 5 to 15°C. The mixture was stirred at room temperature for 1 hour, and the resulting appeared crystals were filtered and washed with methanol (152 /) and then water (152 /). The crystals were dried overnight in vacuo to give 1-(4-methoxycarbonylphenyl)-3-(4-pentyloxyphenyl)propane-1,3-dione
15 (49.6 kg).

NMR (CDCl₃, δ): 0.95 (3H, t, J=1.4Hz), 1.30-1.60 (4H, m), 1.76-1.89 (2H, m), 3.95 (3H, s), 4.03 (2H, t, J=1.3Hz), 6.84 (1H, s), 6.98 (2H, d, J=1.4Hz), 7.99 (2H, d, J=1.4Hz), 8.01 (2H, d, J=1.7Hz), 8.13 (2H, d, J=1.7Hz)
20

MASS (m/z): 369 (M⁺+1)

Preparation 345

Dimethylformamide (123 /), 1-(4-methoxycarbonylphenyl)-
25 3-(4-pentyloxyphenyl)propane-1,3-dione (24.5 kg) and ammonium formate (21.0 kg) were charged in 2000-liter reactor at room temperature and heated, and a reaction was carried out at the inner temperature of 100 to 105°C for 5 hours. After completion of the reaction, the mixture was cooled down to
30 room temperature, ethyl acetate (613 /) and water (613 /) were added, the mixture was stirred, and an ethyl acetate layer was separated, and then washed with 10% sodium chloride solution (613 /) and with 20% sodium chloride solution (613 /). The ethyl acetate layer was concentrated in vacuo to 125
35 / and then diluted with n-heptane (625 /) at the inner

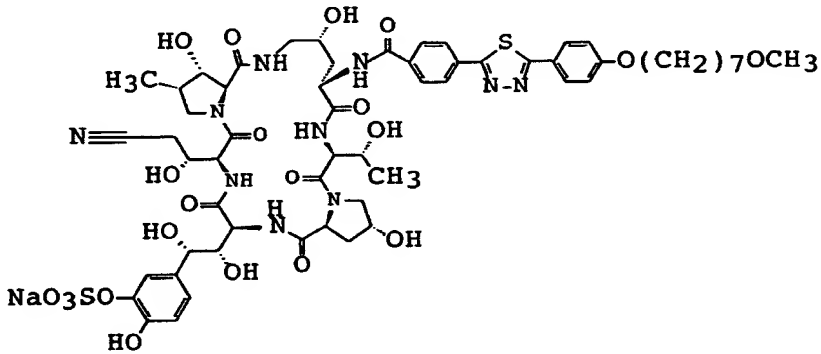
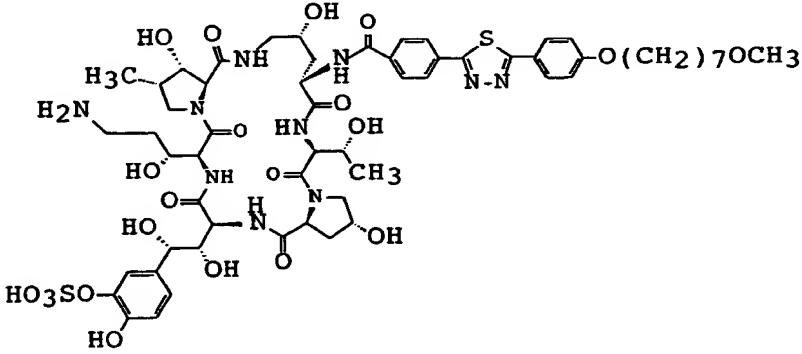
temperature of 40 to 45°C to separate crystals of 1-amino-1-(4-methoxycarbonylphenyl)-3-oxo-3-(4-pentyloxyphenyl)-1-propene. The crystals were filtered at room temperature and washed with a mixture of n-heptane (104 g) and ethyl acetate (21 g). The crystals were dried overnight in vacuo and purified by suspending in a 70% aqueous acetone (158 g) to give 1-amino-1-(4-methoxycarbonylphenyl)-3-oxo-3-(4-pentyloxyphenyl)-1-propene (14.3 kg).

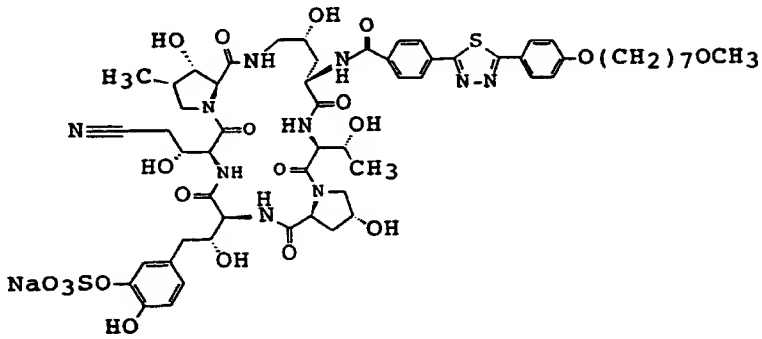
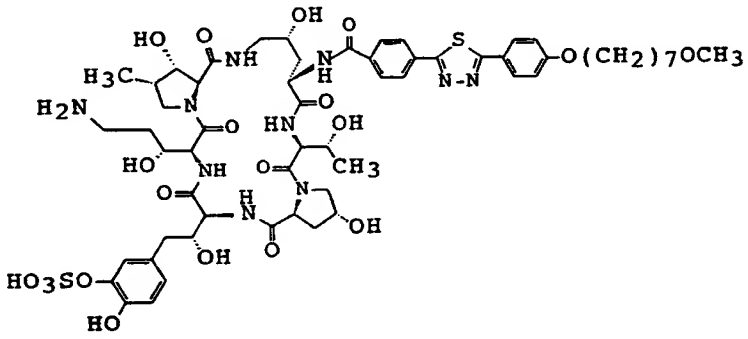
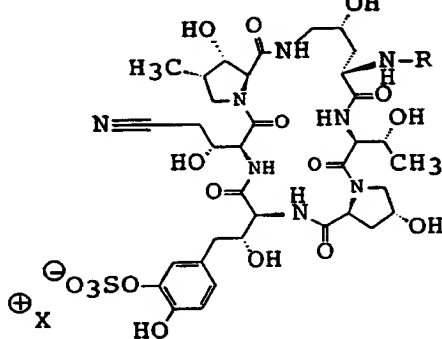
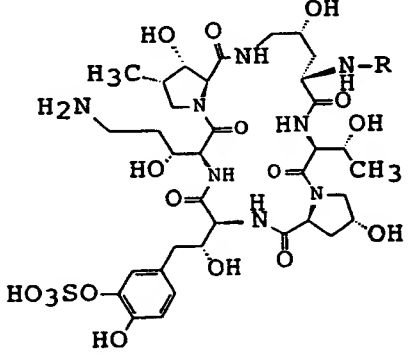
NMR (CDCl₃, δ): 0.94 (3H, t, J=1.4Hz), 1.30-1.55 (4H, m), 1.70-1.90 (2H, m), 3.96 (3H, s), 4.01 (2H, t, J=1.3Hz), 6.13 (1H, br s), 6.92 (2H, d, J=1.8Hz), 7.70 (2H, d, J=1.7Hz), 7.92 (2H, d, J=1.8Hz), 8.13 (2H, d, J=1.7Hz)

MASS (m/z): 368 (M⁺+1)

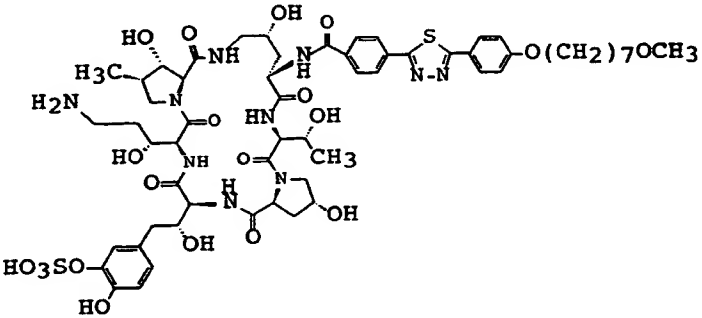
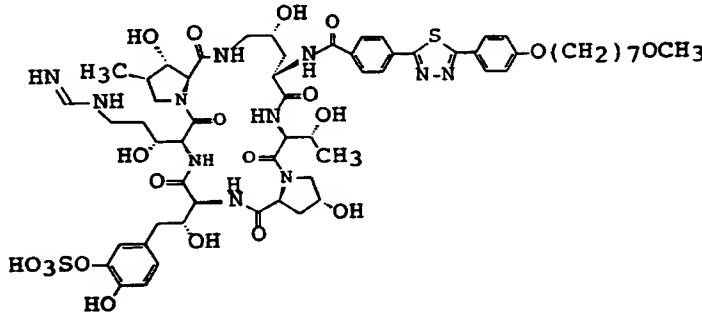
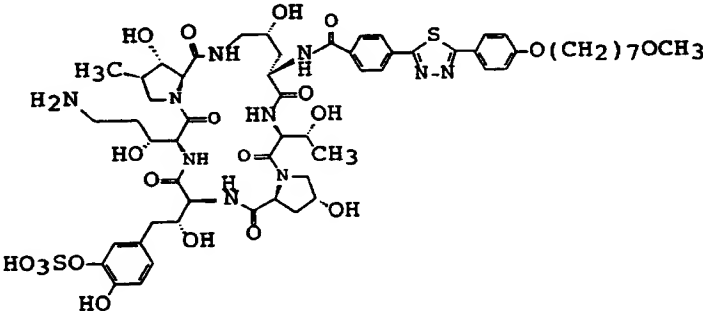
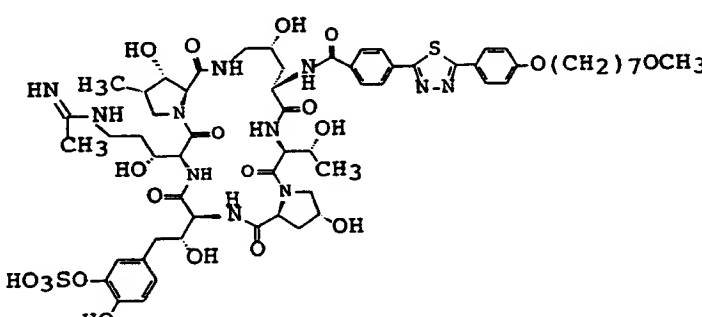
to be continued on the next page

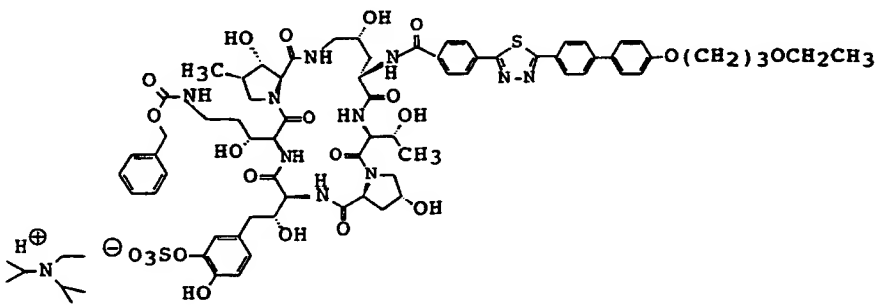
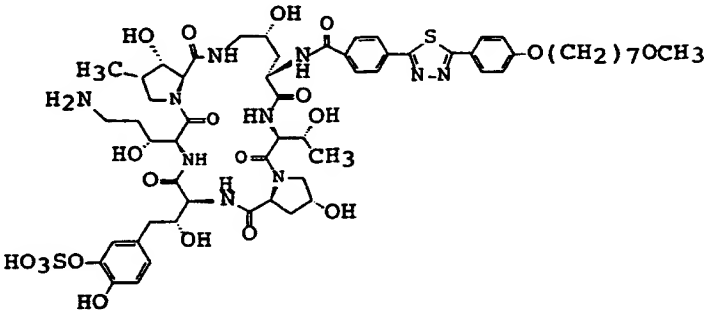
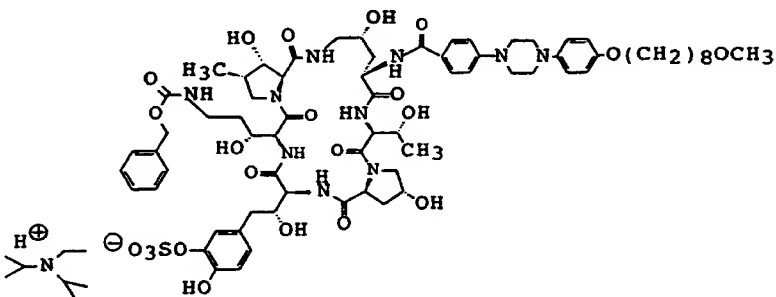
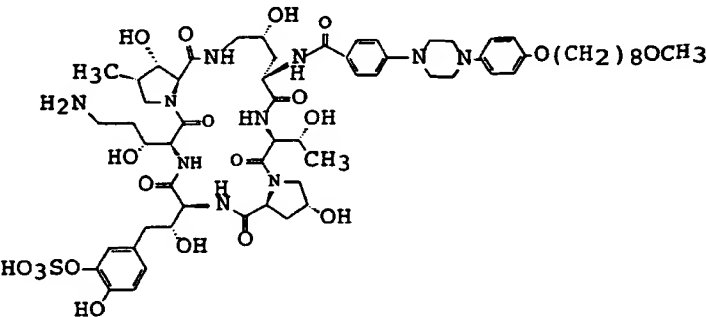
The Starting Compounds used and the Object Compounds obtained in the following Examples 1 to 17 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

Example No.	Formula
1	
	

Example No.	Formula
2	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a nitrile group, and a sulfonate group (NaO₃SO-) attached to a phenyl ring. The molecule also contains a thiazole ring and a long alkoxy chain (O(CH₂)₇OCH₃).</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a sulfonic acid group (HO₃SO-) instead of the sodium sulfonate group.</p>
3 (13	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a sulfonate group (O₃SO⁻) and a variable R group (N-R) attached to the thiazole ring.</p>
	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a sulfonic acid group (HO₃SO-) and a variable R group (N-R) attached to the thiazole ring.</p>

Example No.	R	X
3		Na
4		Na
5		Na
6		Na
7		
8		
9		Na
10		Na
11		Na
12		
13		Na

Example No.	Formula
14	
	
15	
	

Example No.	Formula
16	 <p>Chemical structure of a complex molecule, likely a nucleoside derivative, featuring a central core with multiple hydroxyl groups and a long side chain ending in a triethylammonium cation and a sulfonate anion. The side chain includes a phenyl ring, a thiazole ring, and a long alkyl chain with a terminal triethylammonium group.</p>
	 <p>Chemical structure of a complex molecule, likely a nucleoside derivative, featuring a central core with multiple hydroxyl groups and a long side chain ending in a triethylammonium cation and a sulfonate anion. The side chain includes a phenyl ring, a thiazole ring, and a long alkyl chain with a terminal triethylammonium group.</p>
17	 <p>Chemical structure of a complex molecule, likely a nucleoside derivative, featuring a central core with multiple hydroxyl groups and a long side chain ending in a triethylammonium cation and a sulfonate anion. The side chain includes a phenyl ring, a thiazole ring, and a long alkyl chain with a terminal triethylammonium group.</p>
	 <p>Chemical structure of a complex molecule, likely a nucleoside derivative, featuring a central core with multiple hydroxyl groups and a long side chain ending in a triethylammonium cation and a sulfonate anion. The side chain includes a phenyl ring, a thiazole ring, and a long alkyl chain with a terminal triethylammonium group.</p>

Example 1

A solution of crude Starting compound (5.6 g) in methanol (168 ml) - water (336 ml) was treated with cobalt chloride hexahydrate (3.08 g) and the mixture stirred to give a pink colored solution. Sodium borohydride (2.46 g) was then added portionwise over 1 hour. Additional cobalt chloride (1.54 g) was added followed by sodium borohydride (1.23 g, portionwise). After a total reaction time of 2 hours 50% aqueous acetonitrile (600 ml) was added and insoluble material removed by filtration. The filtrate was evaporated to remove organic solvent and sufficient 1N-sodium hydroxide was added to the remaining aqueous layer to effect solution. This clear aqueous solution was then purified by ODS column chromatography eluting with aqueous acetonitrile. Object compounds-containing fractions were pooled, evaporated, and lyophilized to give Object compound (1.4 g) as an amorphous white powder.

IR (KBr): 1658.5, 1635.3, 1546.6, 1529.3, 1517.7,
1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.10 (3H, d, $J=6\text{Hz}$), 1.30-1.60 (8H, m), 1.60-2.50 (15H, m), 3.21 (3H, s), 2.80-5.40 (29H, m), 6.74 (1H, d, $J=8.2\text{Hz}$), 6.80-6.85 (1H, m), 7.07 (1H, br s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.40-7.80 (4H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.09 (4H, ABq like, br m), 8.20-8.30 (1H, m), 8.80-8.90 (1H, m)

MASS (m/z): 1313.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{78}\text{N}_{10}\text{O}_{21}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 47.34, H 6.16, N 9.52

Found: C 47.42, H 6.26, N 9.47

The following compounds [Examples 2 to 13] were obtained according to a similar manner to that of Example 1.

35 Example 2

IR (KBr): 1648.8, 1631.5, 1538.9, 1515.8, 1442.5,
1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.24 (3H, d,
 $J=5.6\text{Hz}$), 1.40-1.60 (8H, m), 1.60-2.65 (15H, m),
2.80-5.50 (27H, m), 3.21 (3H, s), 3.30 (2H, t,
 $J=6.3\text{Hz}$), 6.72 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, dd,
 $J=1.6$ and 8.3Hz), 7.00 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H,
d, $J=8.9\text{Hz}$), 7.46 (1H, d, $J=8.1\text{Hz}$), 7.60-7.90 (2H,
m), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.04-8.14 (4H, m), 8.24-
8.27 (1H, m), 8.70-9.00 (2H, m)

MASS (m/z): 1297.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{78}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 7.5\text{H}_2\text{O}$:

C 48.56, H 6.53, N 9.76

Found: C 48.56, H 6.31, N 9.63

Example 3

IR (KBr): 1633.4, 1517.7, 1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.13 (3H, d,
 $J=5.7\text{Hz}$), 1.20-1.65 (10H, m), 1.65-2.65 (15H, m),
2.70-5.50 (27H, m), 3.21 (3H, s), 4.07 (2H, t,
 $J=6.5\text{Hz}$), 6.71 (1H, d, $J=8\text{Hz}$), 6.75-6.80 (1H, m),
6.98 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.46
(1H, d, $J=8\text{Hz}$), 7.55-7.85 (2H, m), 7.97 (2H, d,
 $J=8.8\text{Hz}$), 8.07 (4H, ABq, $J=10.8\text{Hz}$), 8.09-8.13 (1H,
m), 8.79 (1H, d, $J=7.9\text{Hz}$), 8.55-9.00 (1H, br s)

MASS (m/z): 1311.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{80}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 10\text{H}_2\text{O}$:

C 47.45, H 6.75, N 9.38

Found: C 47.68, H 6.27, N 9.21

Example 4

IR (KBr): 1648.8, 1631.5, 1540.8, 1513.8, 1452.1 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.6\text{Hz}$), 1.07 (3H, d,
 $J=6\text{Hz}$), 1.1-2.7 (21H, m), 2.7-5.5 (32H, m), 6.68-
6.74 (2H, m), 6.9-6.94 (1H, m), 7.13 (2H, d,

$J=8.9\text{Hz}$), 7.2-7.5 (1H, m), 7.5-7.8 (2H, m), 7.97
(2H, d, $J=8.8\text{Hz}$), 8.09 (4H, s), 8.29 (1H, d,
 $J=7.3\text{Hz}$), 8.5-8.9 (2H, m)
MASS (m/z): 1283.3 (M^+-1)

5

Example 5

IR (KBr): 1635.3, 1531.2, 1444.4, 1251.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d,
 $J=6\text{Hz}$), 1.40-5.30 (41H, m), 3.67-3.70 (2H, m),
4.15-4.23 (2H, m), 6.66 (1H, d, $J=8\text{Hz}$), 6.64-6.72
(1H, m), 6.96 (1H, br s), 7.09 (2H, d, $J=8.9\text{Hz}$),
7.4-7.8 (4H, m), 7.57 (2H, d, $J=6.3\text{Hz}$), 7.74 (2H,
d, $J=8.8\text{Hz}$), 8.0-8.3 (7H, m), 8.73 (1H, d, $J=7.5\text{Hz}$)

10

MASS (m/z): 1304.3 (M^+)

15

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{72}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 11\text{H}_2\text{O}$:

C 47.13, H 6.30, N 9.32

Found: C 47.22, H 5.90, N 8.82

Example 6

20

IR (KBr): 1635.3, 1531.2, 1508.1, 1444.4, 1251.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d,
 $J=5.4\text{Hz}$), 1.3-5.3 (44H, m), 3.25 (3H, s), 4.05 (2H,
t, $J=6\text{Hz}$), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.75-6.79 (1H,
m), 6.96 (1H, br s), 7.07 (2H, d, $J=8.9\text{Hz}$), 7.4-7.8
(4H, m), 7.73 (2H, d, $J=8.8\text{Hz}$), 7.87 (2H, d,
 $J=8.5\text{Hz}$), 8.08-8.16 (7H, m), 8.7-8.8 (1H, m)

25

MASS (m/z): 1332.4 (M^+)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{76}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 11\text{H}_2\text{O}$:

C 47.84, H 6.45, N 9.15

Found: C 48.10, H 6.00, N 8.94

30

Example 7

IR (KBr): 1635.3, 1606.4, 1531.2, 1496.5, 1444.4,
1419.4 cm^{-1}

35

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.11 (3H, d,

J=5.7Hz), 1.05-1.04 (5H, m), 1.50-5.30 (52H, complex m), 6.67 (1H, d, J=5.7Hz), 6.73-6.80 (1H, m), 7.01 (1H, d, J=1.6Hz), 7.08 (2H, d, J=9Hz), 7.4-7.8 (3H, m), 7.85 (2H, d, J=8.7Hz), 8.07 (4H, ABq, J=9Hz), 8.31 (1H, d, J=6.9Hz), 8.71 (1H, s), 8.91 (1H, d, J=7.4Hz)

MASS (m/z): 1319.4 (M^+-1)

Elemental Analysis Calcd. for $C_{60}H_{80}N_{12}O_{18}S_2 \cdot 9H_2O$:

C 48.57, H 6.66, N 11.33

Found: C 48.77, H 6.54, N 11.25

Example 8

IR (KBr): 1635.3, 1529.3, 1519.6, 1467.6, 1446.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.91 (3H, t, J=7Hz), 0.96 (3H, d, J=8.3Hz), 1.12 (3H, d, J=5.6Hz), 1.2-2.6 (17H, m), 2.6-5.4 (29H, m), 6.71 (1H, d, J=8Hz), 6.77 (1H, br d, J=8Hz), 6.98 (1H, d, J=1.7Hz), 7.14 (2H, d, J=8.9Hz), 7.45 (1H, d, J=8.5Hz), 7.4-7.8 (3H, m), 7.90 (2H, d, J=8.8Hz), 8.05 (4H, s), 8.1-8.3 (1H, s), 8.64 (1H, d, J=6.9Hz), 8.85 (1H, s)

MASS (m/z): 1278.3 (M^+-1)

Elemental Analysis Calcd. for $C_{57}H_{73}N_{11}O_{19}S_2 \cdot 9H_2O$:

C 47.46, H 6.36, N 10.68

Found: C 47.58, H 6.17, N 10.62

Example 9

IR (KBr): 3361.3, 2937.1, 1635.3, 1523.5, 1461.8, 1251.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.8Hz), 1.10 (3H, d, J=5.9Hz), 1.2-5.3 (49H, m), 6.67-6.80 (2H, m), 7.01 (1H, d, J=1.6Hz), 7.15 (2H, d, J=9Hz), 7.4-7.8 (3H, m), 7.88 (2H, d, J=8.8Hz), 7.96 (4H, s), 8.35 (1H, d, J=8.3Hz), 8.7-8.8 (2H, m), 8.86 (1H, s)

API-ES MASS (Negative): 1290.3 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{73}N_{11}O_{19}S_2 \cdot 8H_2O$:

C 48.29 H 6.26, N 10.53

Found: C 48.49 H 6.24, N 10.73

5 Example 10

IR (KBr): 1637.3, 1523.5, 1459.9, 1238.1 cm^{-1}

MASS (m/z): 1358.4 (M^+-1)

Example 11

10 IR (KBr): 3357.5, 1631.5, 1517.7, 1465.6, 1450.2,
1241.9 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8Hz$), 1.10 (3H, d,
 $J=6Hz$), 1.18 (6H, d, $J=6Hz$), 1.5-2.7 (11H, m), 2.8-
5.4 (33H, m), 6.71 (1H, d, $J=8.2Hz$), 6.78 (1H, dd,
15 $J=8$ and $1.6Hz$), 7.01 (1H, d, $J=1.6Hz$), 7.12 (2H, d,
 $J=9Hz$), 7.44 (1H, d, $J=8.7Hz$), 7.6-7.9 (1H, m),
7.67 (1H, d, $J=8Hz$), 7.78 (2H, d, $J=8.8Hz$), 7.96
(4H, s), 8.35 (1H, d, $J=7Hz$), 7.6-8.8 (1H, br s),
8.75 (1H, d, $J=7Hz$), 8.81 (1H, s)

20 API-ES MASS (Negative): 1305.3 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{74}N_{12}O_{19}S_2 \cdot 8H_2O$:

C 48.05, H 6.24, N 11.55

Found: C 47.99, H 6.25, N 11.58

25 Example 12

IR (KBr): 1631.5, 1510.0, 1446.4, 1234.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7Hz$), 1.09 (3H, d,
 $J=5.8Hz$), 1.2-2.65 (15H, m), 2.7-5.3 (41H, m), 3.21
(3H, s), 3.30 (2H, t, $J=6.4Hz$), 3.85 (2H, t,
30 $J=6.5Hz$), 6.70 (1H, d, $J=8.2Hz$), 6.74-6.80 (1H, m),
6.83 (2H, d, $J=9Hz$), 6.94 (2H, d, $J=9Hz$), 6.99 (1H,
s), 7.01 (2H, d, $J=8.8Hz$), 7.44 (1H, d, $J=8.6Hz$),
7.6-7.9 (2H, m), 7.80 (2H, d, $J=8.7Hz$), 8.1-8.3
(2H, m), 8.37 (1H, d, $J=7.7Hz$)

35 MASS (m/z): 1297.5 (M^+-Na)

Elemental Analysis Calcd. for $C_{60}H_{86}N_{10}O_{20}S \cdot 7H_2O$:

C 50.55, H 7.07, N 9.83

Found: C 50.68, H 7.08, N 9.82

5 Example 13

IR (KBr): 1648.8, 1631.5, 1540.8, 1511.9, 1454.1,
1238.1 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.8-1.3 (18H, m), 1.5-2.5 (24H, m),
2.61 (4H, br s), 2.8-5.4 (27H, m), 6.70 (1H, d,
J=8.1Hz), 6.77 (1H, br d, J=10Hz), 6.92 (2H, d,
J=9Hz), 7.00 (1H, d, J=1.6Hz), 7.42 (1H, d,
J=8.6Hz), 7.5-7.7 (2H, m), 7.76 (2H, d, J=8.6Hz),
8.30 (1H, d, J=7.1Hz), 8.44 (1H, d, J=6.9Hz), 8.46-
9.00 (1H, br s)

15 MASS (m/z): 1241.3 ($M^+ - 1$)

Elemental Analysis Calcd. for $C_{58}H_{86}N_{10}O_{18}S \cdot 10H_2O$:

C 48.94, H 7.50, N 9.84

Found: C 49.19, H 7.33, N 9.73

20 Example 14

A solution of Starting compound (150 mg) in N,N-dimethylformamide (1.5 ml) was treated with diisopropylethylamine (166.5 mg) and ethyl formimidate hydrochloride (64.8 mg) and stirred 2 days at room
25 temperature. Additional ethyl formimidate hydrochloride (39 mg) was added and stirring continued a further 3 hours 15 minutes. The reaction mixture was diluted with water and purified by ODS column chromatography, eluting with aqueous acetonitrile. Product-containing fractions were pooled,
30 evaporated, and lyophilized to give Object compound as an amorphous white powder.

IR (KBr): 1658.5, 1635.3, 1444.4, 1257.4 cm^{-1}

35 NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d, J=6.1Hz), 1.20-1.60 (8H, m), 1.60-2.50 (15H, m),
3.21 (3H, s), 2.80-5.30 (27H, m), 6.71 (1H, d,

J=8.1Hz), 6.78 (1H, d, J=6Hz), 7.00 (1H, br s),
7.14 (2H, d, J=8.9Hz), 7.40-7.84 (4H, m), 7.84 (1H,
s), 7.97 (2H, d, J=8.8Hz), 8.08 (4H, ABq, J=8.9Hz),
8.30-8.40 (2H, m), 8.90-9.10 (2H, m)

5 MASS (m/z): 1325.4 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{79}N_{11}O_{19}S_2 \cdot 8H_2O$:

C 48.29, H 6.64, N 10.68

Found: C 48.01, H 6.34, N 10.38

10 The following compounds [Examples 15 to 17] were
obtained according to a similar manner to that of Example 14.

Example 15

IR (KBr): 1658, 1635, 1628, 1444, 1257 cm^{-1}

15 NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.11 (3H, d,
J=6.1Hz), 1.25-1.60 (8H, m), 1.60-2.50 (15H, m),
2.05 (3H, s), 3.21 (3H, s), 2.80-5.30 (27H, m),
6.71 (1H, d, J=8.1Hz), 6.77 (1H, d, J=8Hz), 7.00
(1H, br s), 7.13 (2H, d, J=8.9Hz), 7.30-7.90 (4H,
20 m), 7.97 (2H, d, J=8.7Hz), 8.08 (4H, ABq, J=8.8Hz),
8.50-9.00 (4H, m)

MASS (m/z): 1362.3 (M^+-Na)

Elemental Analysis Calcd. for $C_{59}H_{81}N_{11}O_{19}S_2 \cdot 9H_2O$:

C 48.06, H 6.77, N 10.45

25 Found: C 48.02, H 6.48, N 10.11

Example 16

IR (KBr): 1643.1, 1633.4, 1535.1, 1513.8, 1442.5,
1249.6 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.8Hz), 1.1-1.16 (3H,

5 m), 1.12 (3H, t, J=7Hz), 1.4-2.6 (12H, m), 2.8-5.2 (34H, m), 6.71 (1H, d, J=8Hz), 6.78 (1H, dd, J=8 and 2Hz), 7.00 (1H, d, J=2Hz), 7.08 (2H, d, J=8.8Hz), 7.45 (1H, d, J=8.9Hz), 7.6-7.8 (2H, m), 7.73 (2H, d, J=8.8Hz), 7.87 (2H, d, J=8.5Hz), 8.0-8.2 (6H, m), 8.28 (1H, d, J=7Hz), 8.91 (1H, d, J=7.6Hz), 8.5-9.05 (1H, br s)

MASS (m/z): 1331.2 (M^+-1)

Elemental Analysis Calcd. for $C_{61}H_{76}N_{10}O_{20}S_2 \cdot 10H_2O$:

10 C 48.41, H 6.39, N 9.25
Found: C 48.63, H 6.13, N 9.13

Example 17

15 IR (KBr): 1631.5, 1537.0, 1510.0, 1448.3, 1234.2 cm^{-1}
NMR (DMSO- d_6 + D_2O , δ): 0.96 (3H, d, J=6.7Hz), 1.05-1.15 (3H, m), 1.2-3.0 (33H, m), 3.15 (3H, s), 3.29 (2H, t, J=6.4Hz), 3.88 (2H, t, J=6.4Hz), 3.6-4.5 (14H, m), 4.7-4.85 (2H, m), 6.73-7.04 (9H, m), 7.75-7.9 (2H, m)

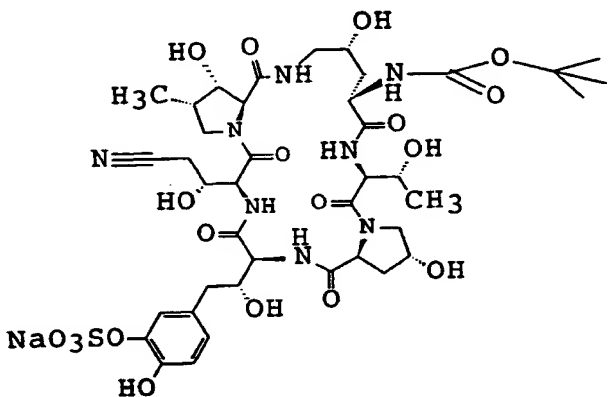
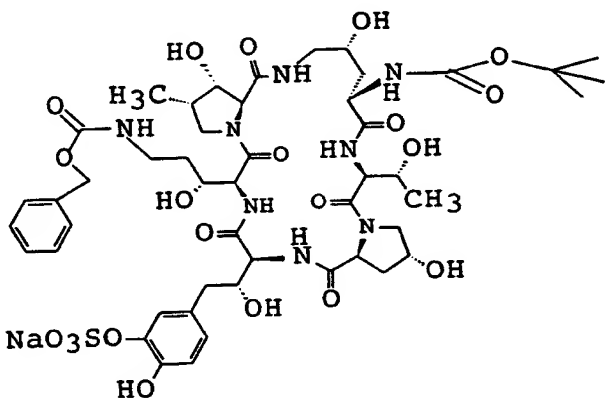
20 MASS (m/z): 1311.4 (M^+-1)

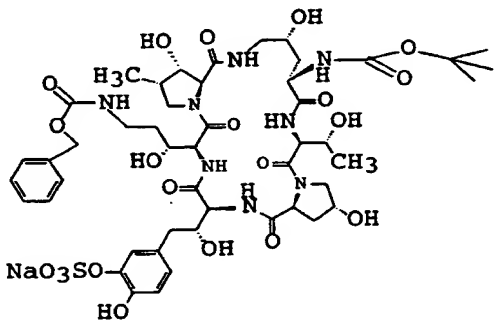
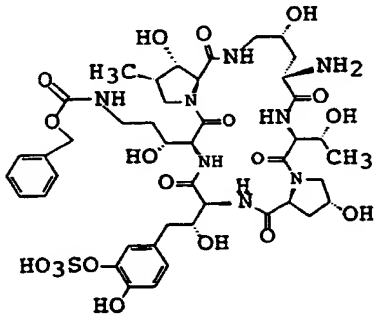
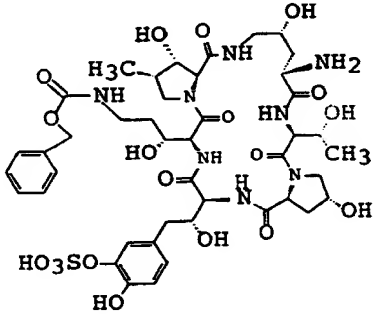
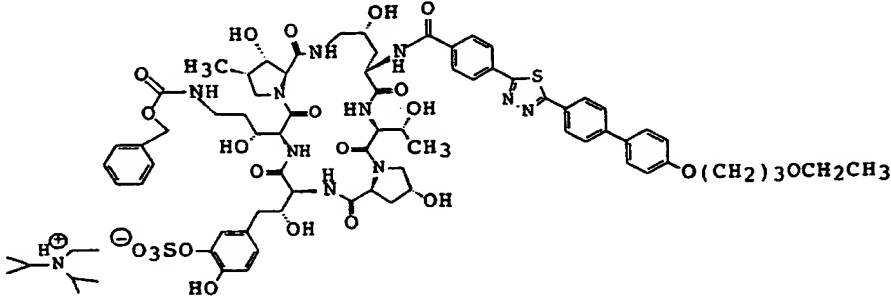
Elemental Analysis Calcd. for $C_{61}H_{88}N_{10}O_{20}S \cdot 10H_2O$:

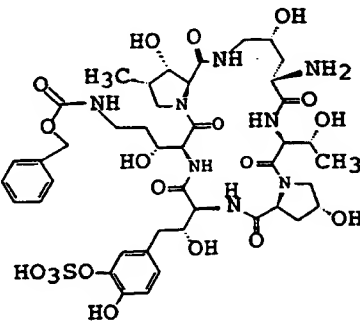
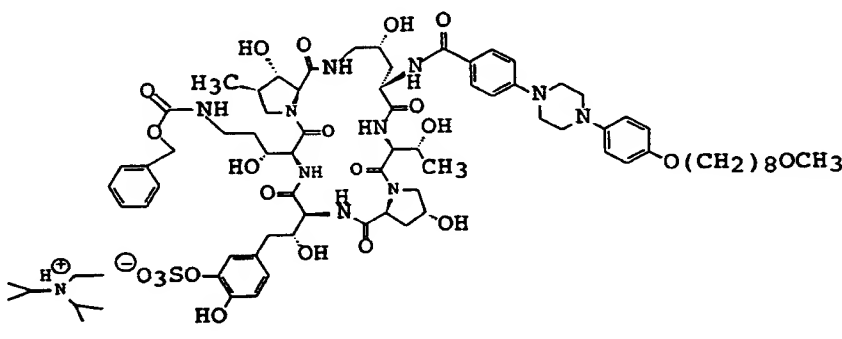
C 49.05, H 7.29, N 9.38
Found: C 48.78, H 6.83, N 9.27

25 The Starting Compounds (18) to (21) used and the Object Compounds (18) to (21) obtained in the following Examples 18 to 21 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column,
30 respectively.

5

Example No.	Formula
18	
	

Example No.	Formula
19	
	
20	
	

Example No.	Formula
21	
	

Example 18

A solution of Starting compound (2.0 g) in methanol (100 ml) - water (20 ml) was treated with cobalt(II) chloride hexahydrate (1.89 g) and then stirred to give a pink solution. Sodium borohydride (1.5 g) was then added portionwise and then stirred for 1 hour at room temperature. The reaction mixture was filtered through a bed of celite, washing with methanol (100 ml) - water (30 ml) solution. The ice-cooled filtrate was then treated dropwise with a solution of benzyloxy carbonyl chloride (Z-chloride) (0.34 ml) in tetrahydrofuran (5 ml) and stirred for 1 hour at the same temperature. Ethyl acetate (50 ml) was added followed by water (200 ml) and after stirring - 5 minutes, the separated organic layer was discarded. The aqueous layer was adjusted to pH 8.8 and evaporated to remove organic solvent and then purified by ODS column chromatography, eluting with aqueous

acetonitrile (10-30%). Object compound containing fractions were pooled, evaporated, and lyophilized to give Object compound (1.61 g) as an amorphous white powder.

IR (KBr): 1666.2, 1631.5, 1517.7, 1444.4, 1267.0 cm^{-1}

5 NMR (DMSO-d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.00-1.15 (3H, m), 1.33 (9H, s), 1.35-2.10 (6H, m), 2.10-2.50 (4H, m), 2.80-3.30 (4H, m), 3.60-4.55 (12H, m), 4.60-4.90 (2H, m), 4.99 (2H, s), 4.50-5.30 (4H, m), 6.60-7.10 (4H, m), 7.33 (5H, s), 7.35-7.90 (3H, m), 8.72 (1H, br s)

10 MASS (m/z): 1123.3 ($M^+-\text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{48}\text{H}_{67}\text{N}_8\text{O}_{21}\text{SNa}\cdot 6\text{H}_2\text{O}$:

C 45.93, H 6.34, N 8.93

Found: C 45.68, H 6.33, N 8.82

15

Example 19

A suspension of Starting compound (1.6 g) in dichloromethane (41 ml) was stirred with cooling at 5°C and treated with triethylsilane (1.1 ml), followed by trifluoroacetic acid (5.3 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, then poured into 450 ml of pH 6.86 phosphate buffer and adjusted to pH 8.5 with 4N-sodium hydroxide solution. Organic solvent was removed by evaporation and the remaining aqueous solution purified by ODS column chromatography, eluting with aqueous acetonitrile (5-20%). Object compound-containing fractions were pooled, evaporated, and lyophilized to give Object compound (1.25 g) as an amorphous white powder.

30 IR (KBr): 1633.4, 1537.0, 1517.7, 1440.6, 1267.0 cm^{-1}

NMR (DMSO-d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, d, $J=5.8\text{Hz}$), 1.27 (2H, d, $J=6.6\text{Hz}$), 1.28-1.70 (2H, m), 1.75-2.45 (4H, m), 2.65-3.30 (5H, m), 3.50-4.50 (11H, m), 4.60-4.90 (2H, m), 5.00 (2H, s), 5.05-5.40 (5H, m), 6.70 (2H, d, $J=8.2\text{Hz}$), 6.76 (2H, d,

35

J=8.2Hz), 6.96 (1H, s), 7.00-7.15 (1H, m), 7.34
(5H, s), 7.40-7.95 (3H, m), 8.60-8.90 (1H, m)

MASS (m/z): 1023.3 ($M^+ - H$)

Elemental Analysis Calcd. for $C_{43}H_{60}N_8O_{19}S \cdot 6H_2O$:

C 45.58, H 6.40, N 9.89

Found: C 45.49, H 6.24, N 9.70

Example 20

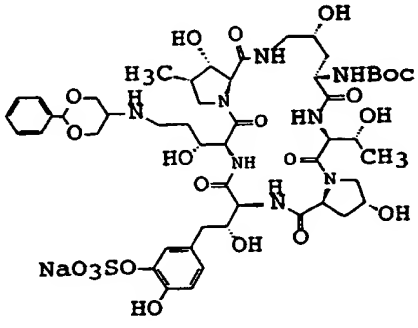
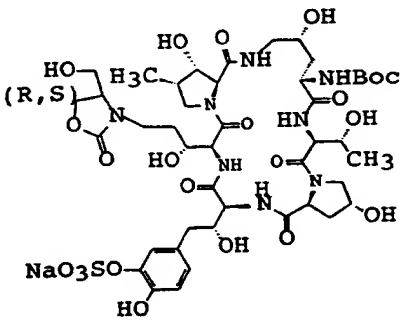
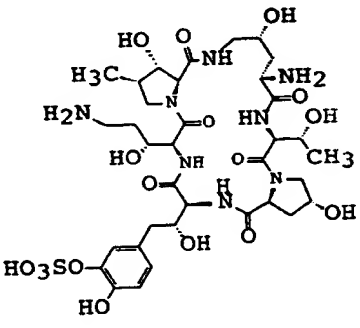
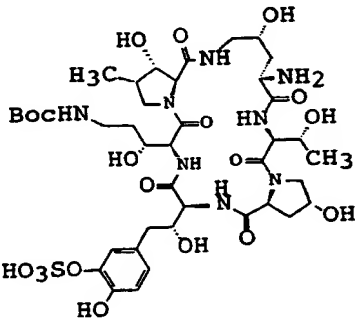
NMR (DMSO- d_6 , δ): 0.95 (3H, d, J=6.6Hz), 6.67 (1H, d,
J=6.9Hz), 6.73-6.75 (1H, m), 6.96 (1H, br s), 7.07
(2H, d, J=8.8Hz), 7.32 (5H, s), 7.73 (2H, d,
J=8.7Hz), 7.87 (2H, d, J=8.5Hz), 8.06-8.14 (6H, m),
8.72 (1H, s), 8.80 (1H, d, J=7.1Hz)

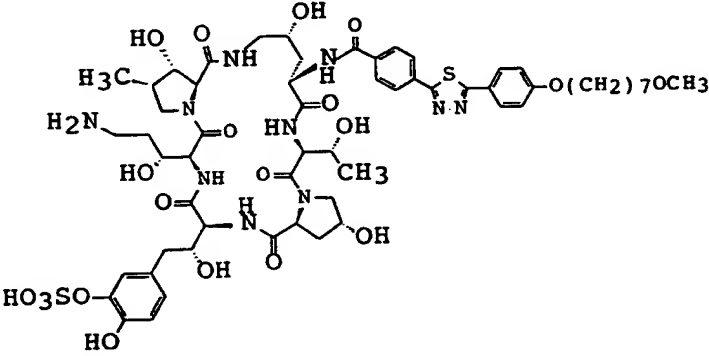
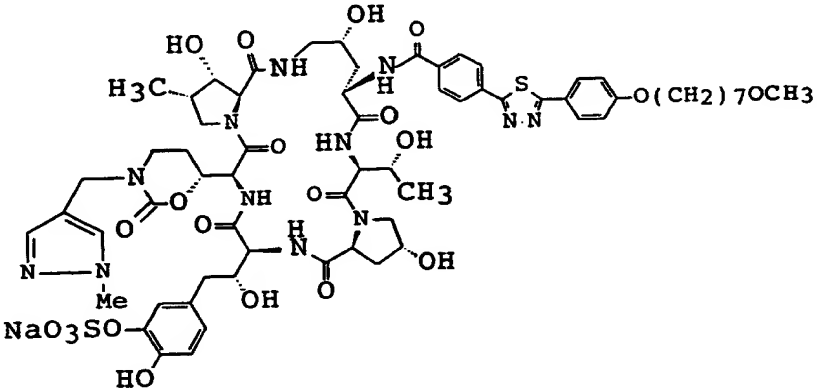
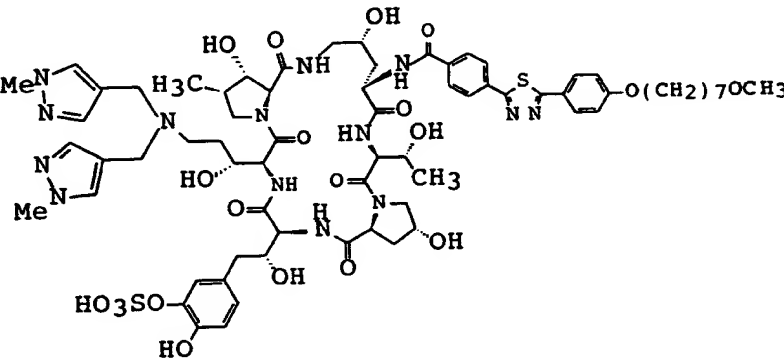
MASS (m/z): 1465.5 ($M^+ - Na$)

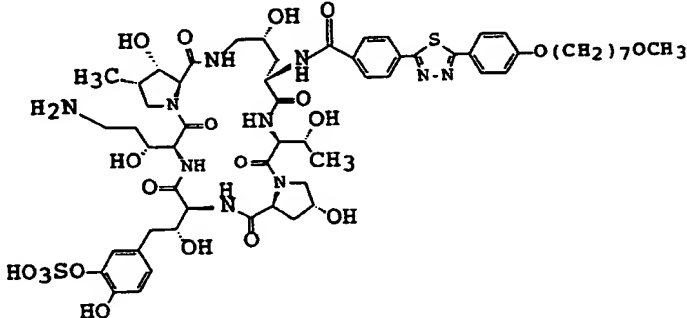
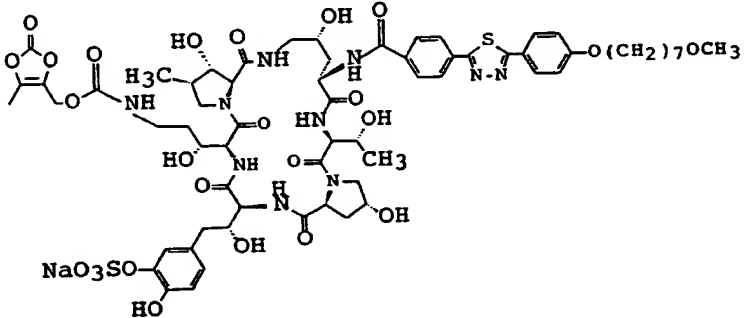
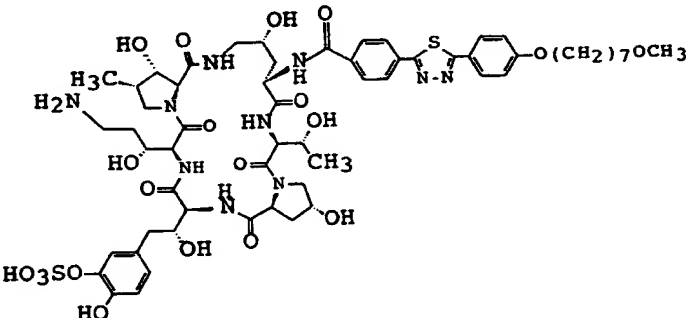
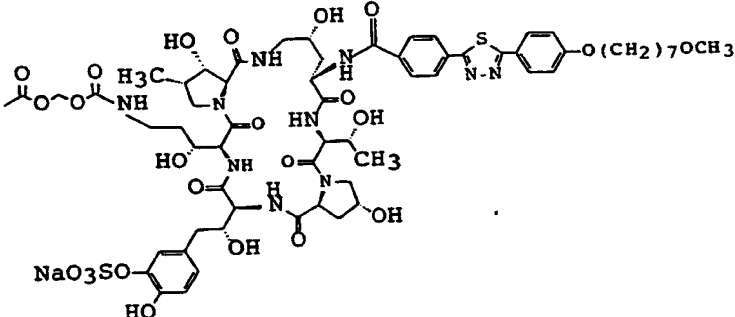
Example 21

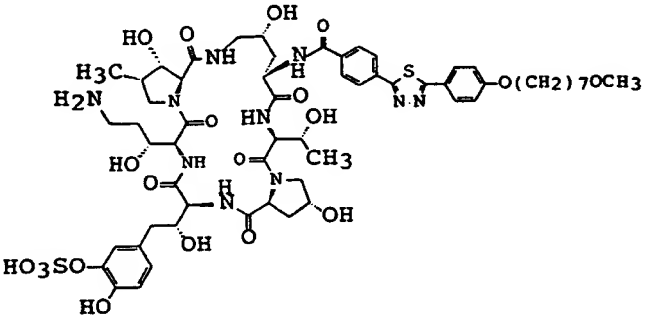
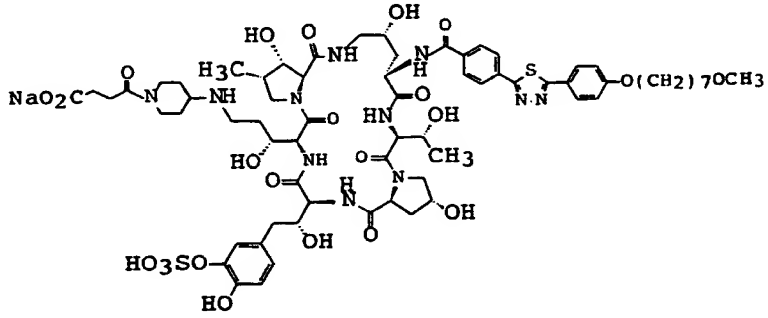
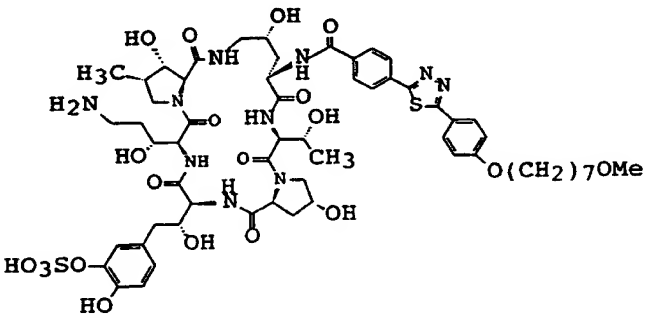
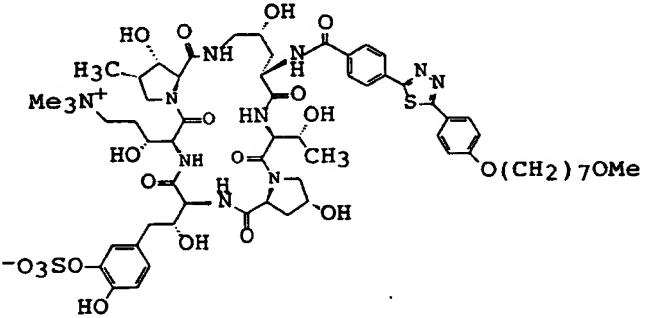
The Object Compound (21) was used directly in the next
reaction without purification.

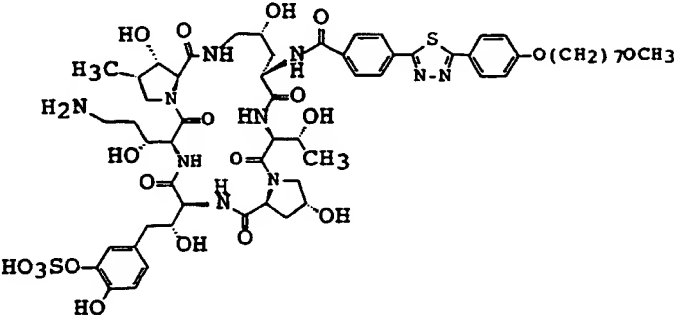
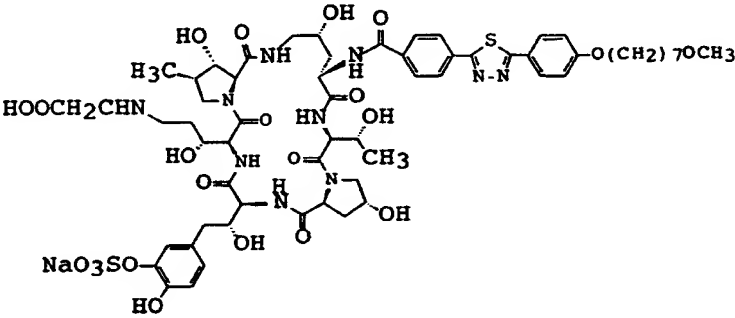
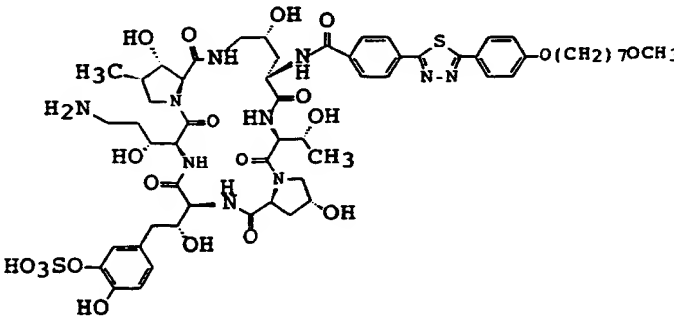
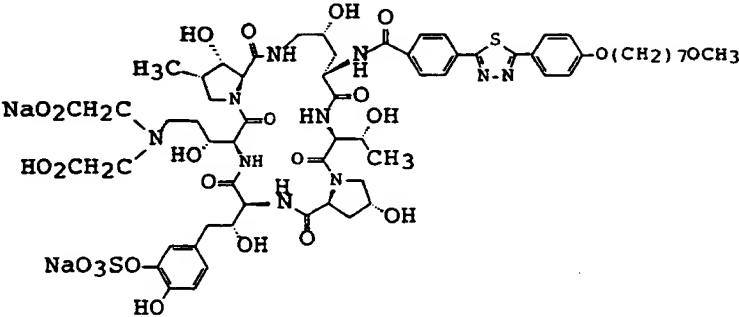
The Starting Compounds (22) to (206) used and the Object
Compounds (22) to (206) obtained in the following Example 22
to 206 are given in the table as below, in which the formulas
of the starting compounds are in the upper column and the
formulas of the object compounds are in the lower column,
respectively.

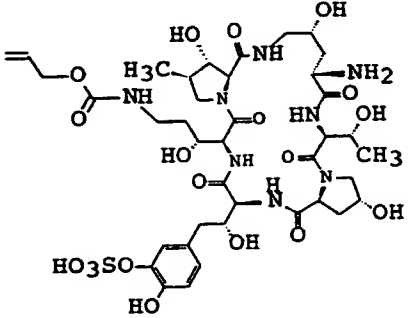
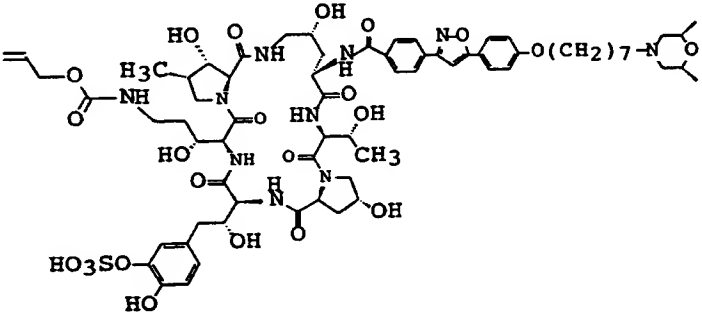
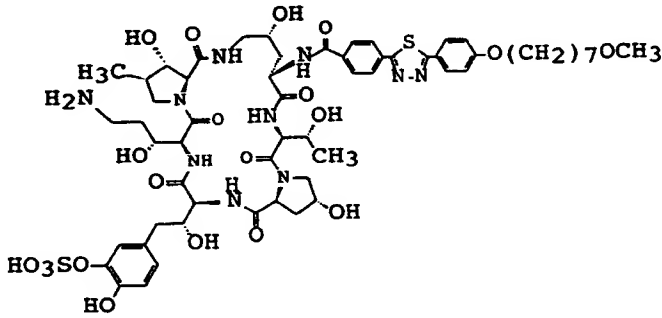
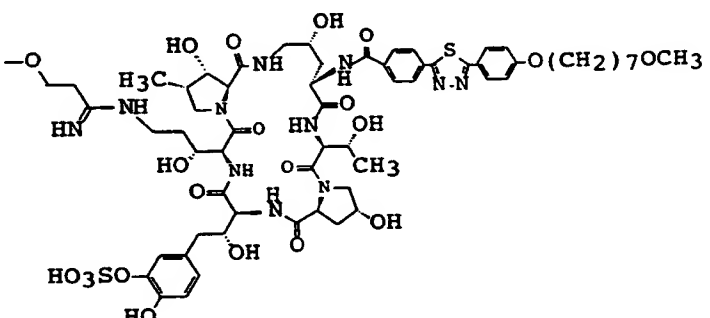
Example No.	Formula
22	
	
23	
	

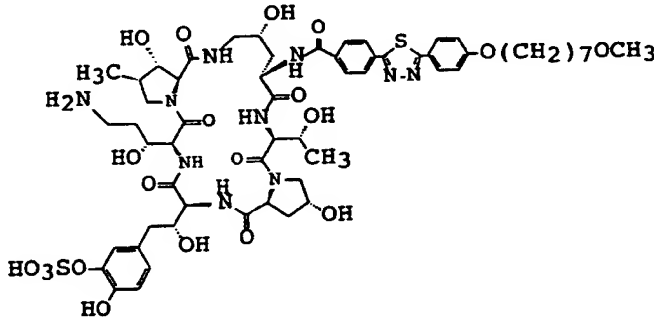
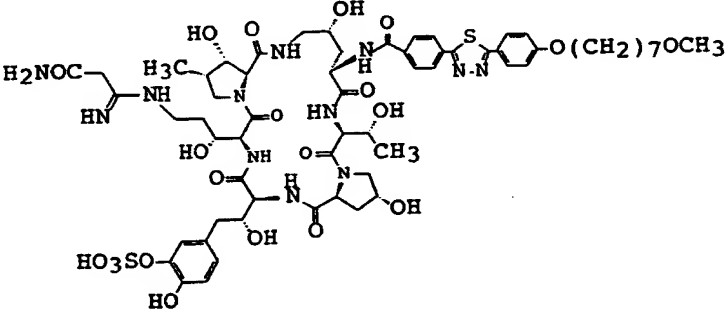
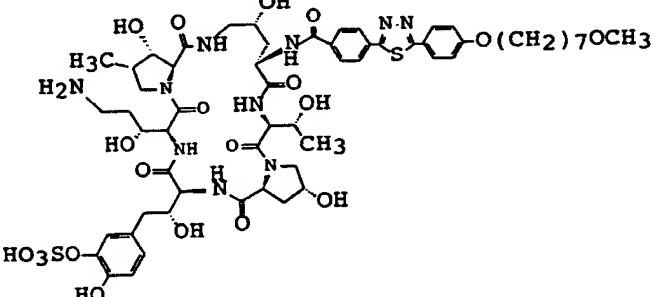
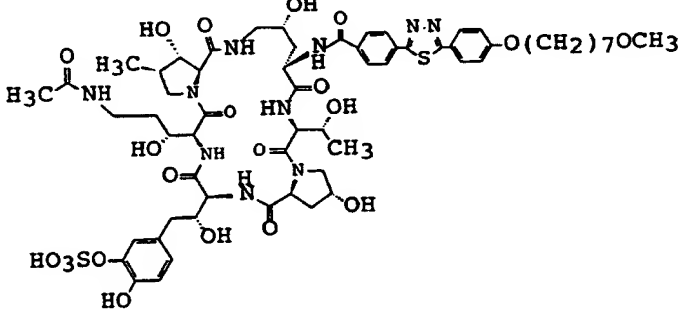
Example No.	Formula
24	
	 

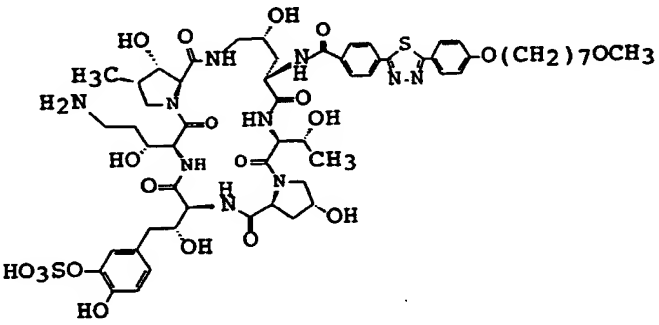
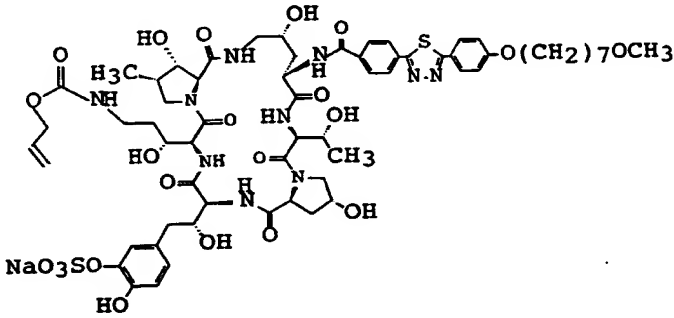
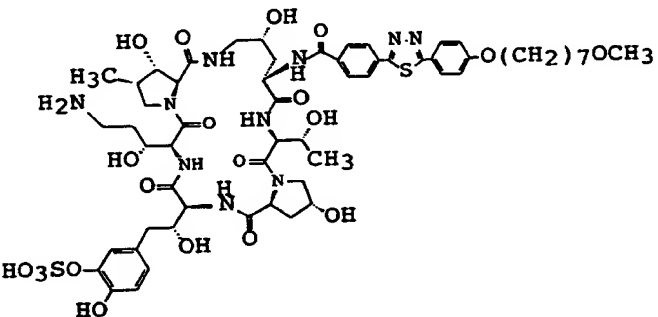
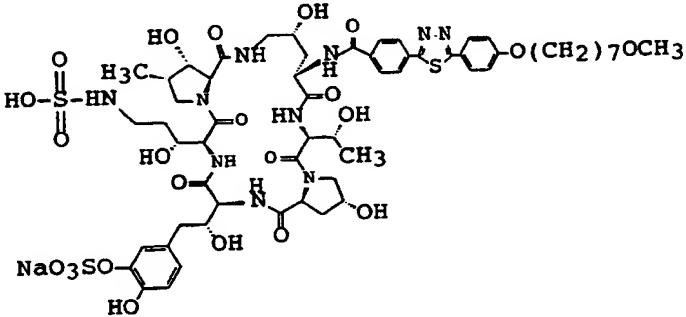
Example No.	Formula
25	 <p>Chemical structure of Example 25, top formula: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sulfonamide group. It is substituted with a 4-(4-hydroxyphenyl)-3-sulfamoylphenyl group and a 4-(4-methoxyphenyl)-1,3,4-oxadiazol-5-yl group.</p>
	 <p>Chemical structure of Example 25, bottom formula: Similar to the top formula, but with a different substitution pattern on the central core, including a sodium sulfonate group and a different ester linkage.</p>
26	 <p>Chemical structure of Example 26, top formula: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sulfonamide group. It is substituted with a 4-(4-hydroxyphenyl)-3-sulfamoylphenyl group and a 4-(4-methoxyphenyl)-1,3,4-oxadiazol-5-yl group.</p>
	 <p>Chemical structure of Example 26, bottom formula: Similar to the top formula, but with a different substitution pattern on the central core, including a sodium sulfonate group and a different ester linkage.</p>

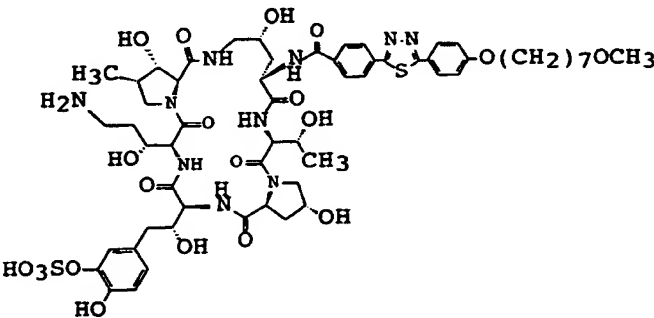
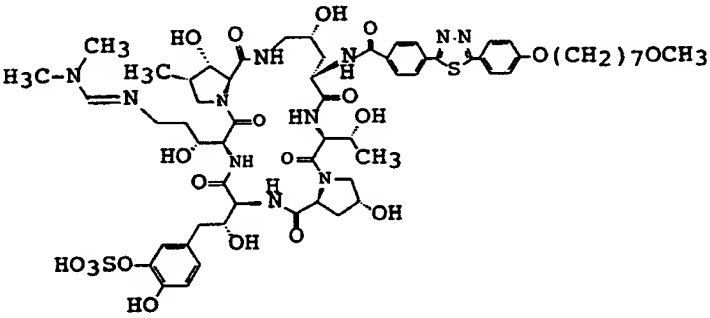
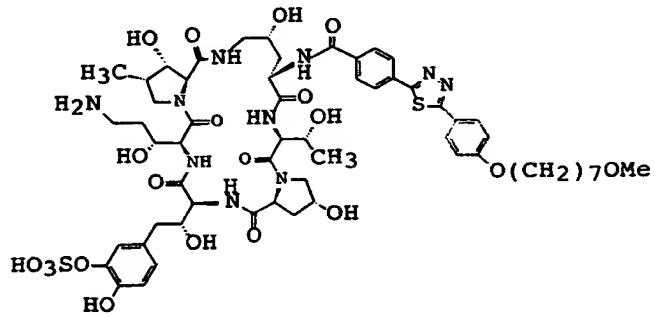
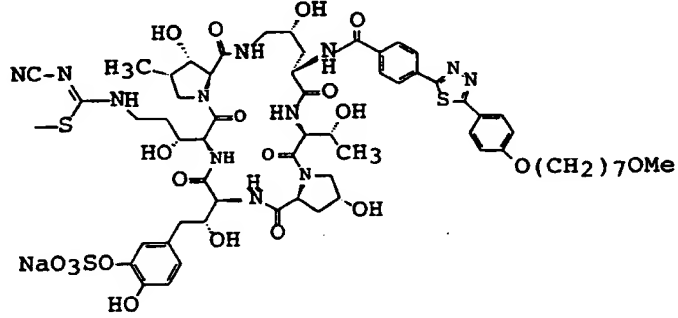
Example No.	Formula
27	 <p>Chemical structure of a complex molecule, likely a derivative of a natural product, featuring a central bicyclic core with multiple hydroxyl groups, a sulfonamide group, and a long alkoxy chain.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different side chain.</p>
28	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different side chain.</p>
	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different side chain.</p>

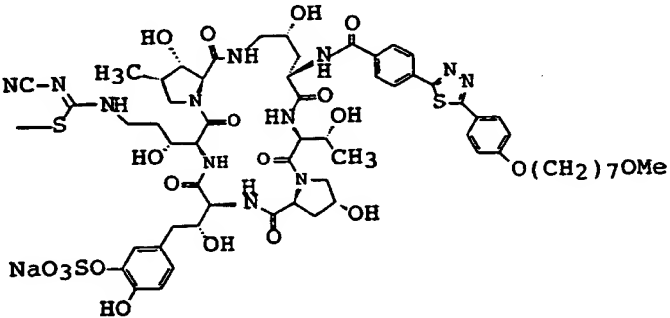
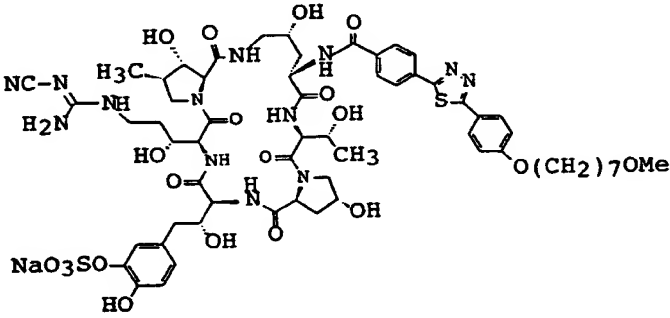
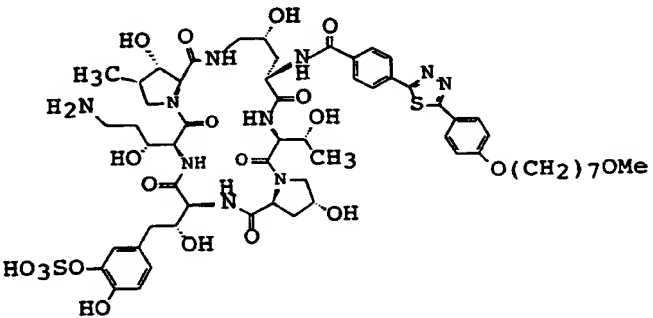
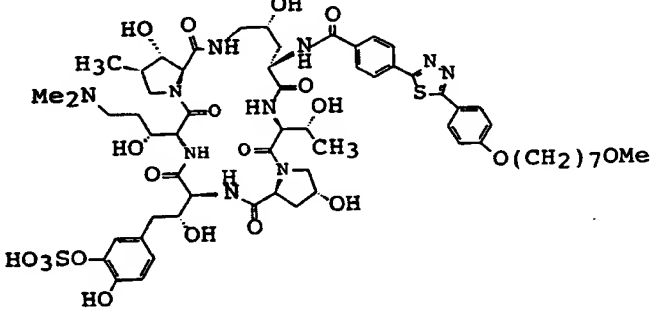
Example No.	Formula
29	
	
30	
	

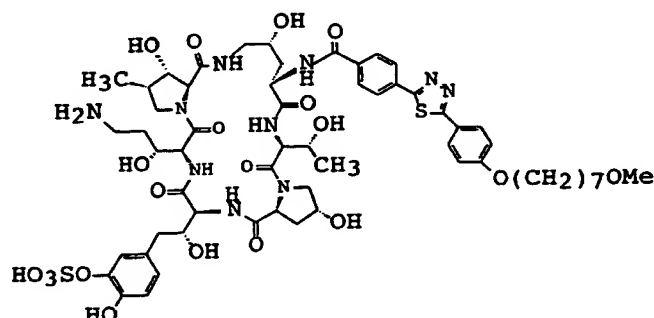
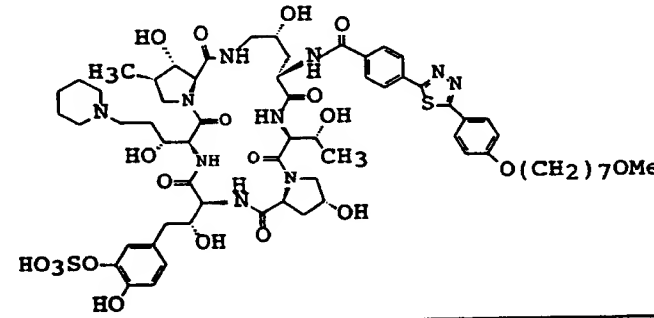
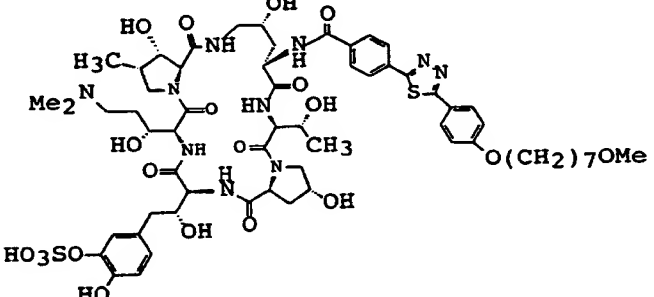
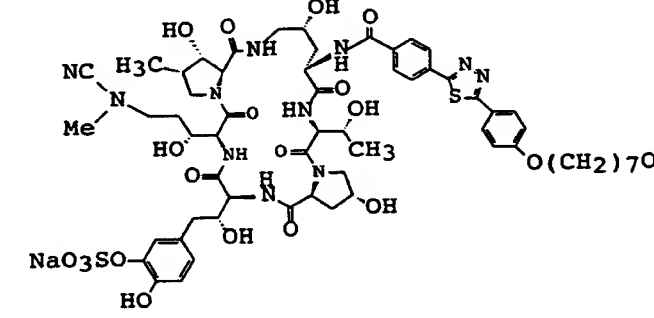
Example No.	Formula
31	
	
32	
	

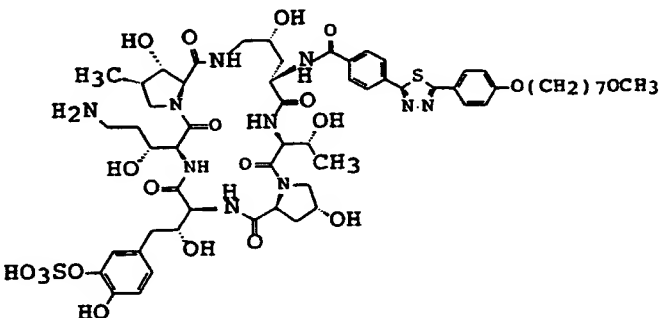
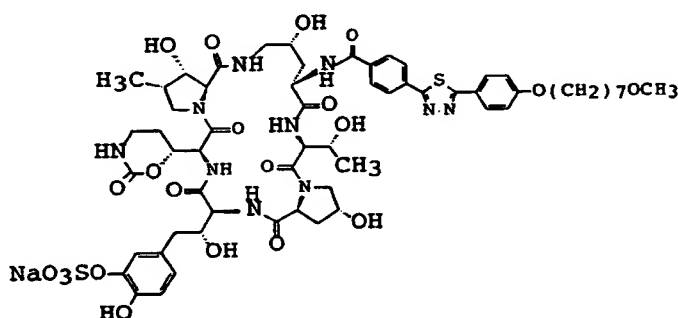
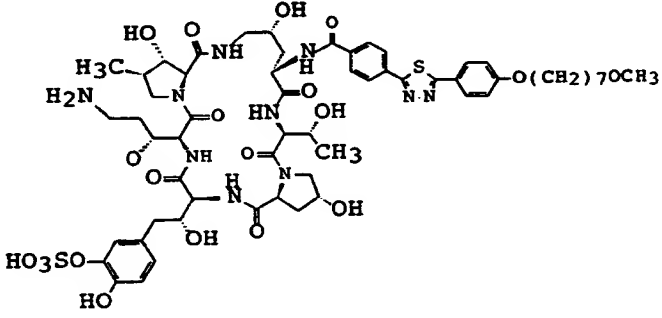
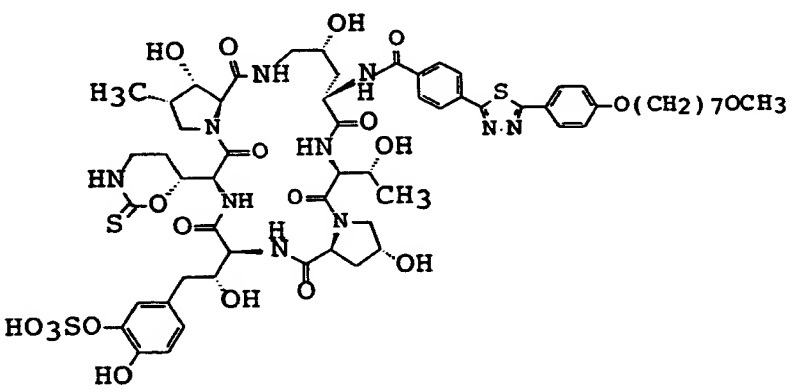
Example No.	Formula
33	
	
34	
	

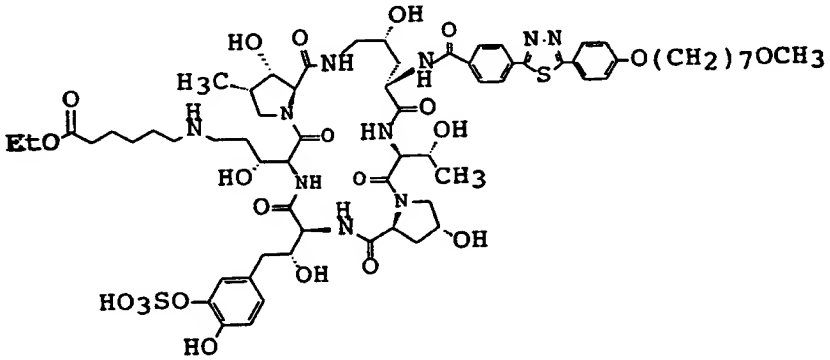
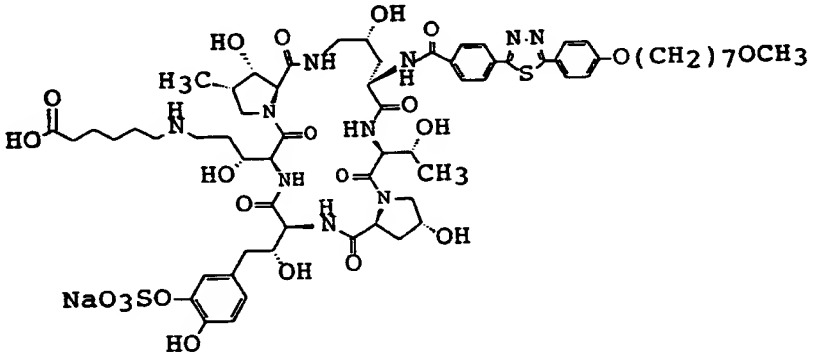
Example No.	Formula
35	
	
36	
	

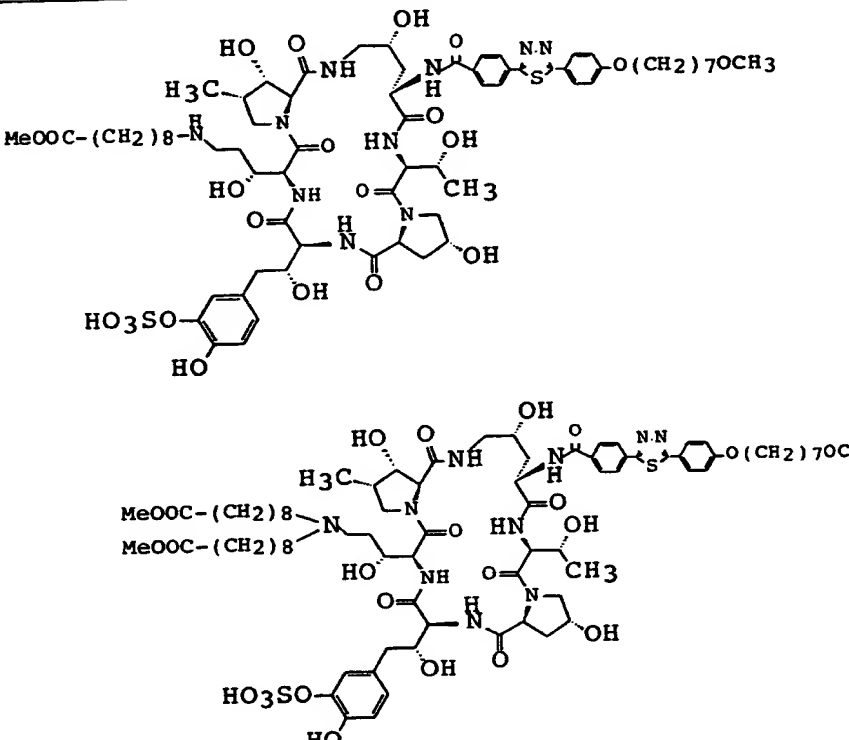
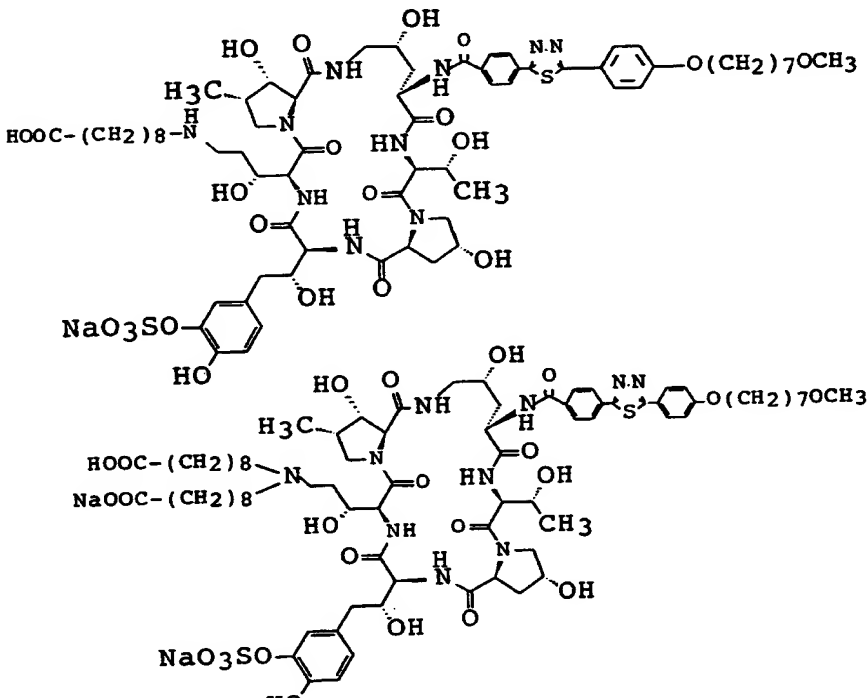
Example No.	Formula
37	
	
38	
	

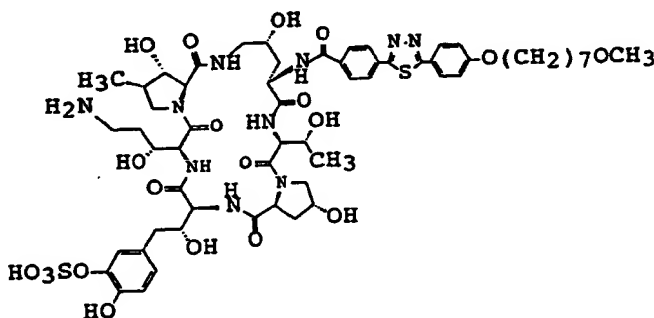
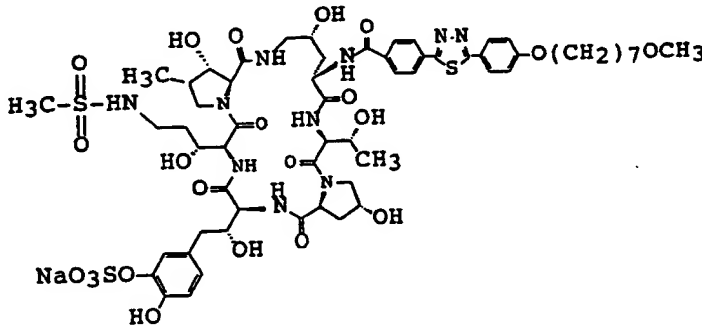
Example No.	Formula
39	
	
40	
	

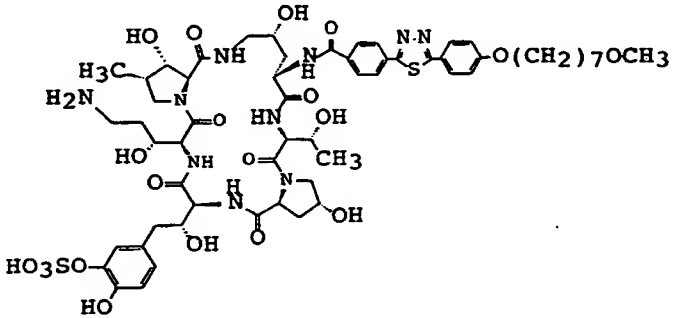
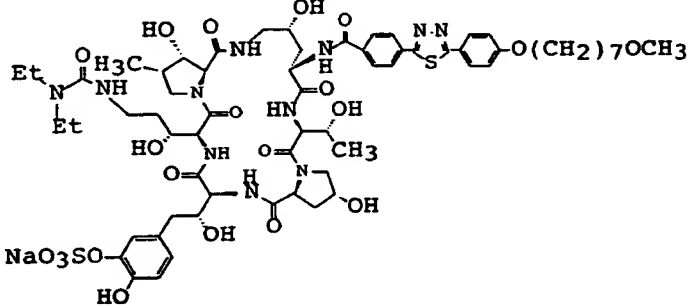
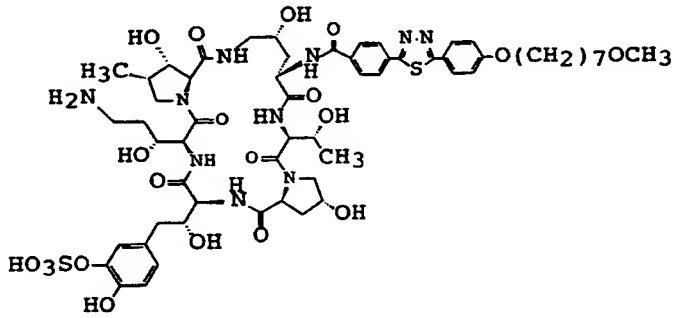
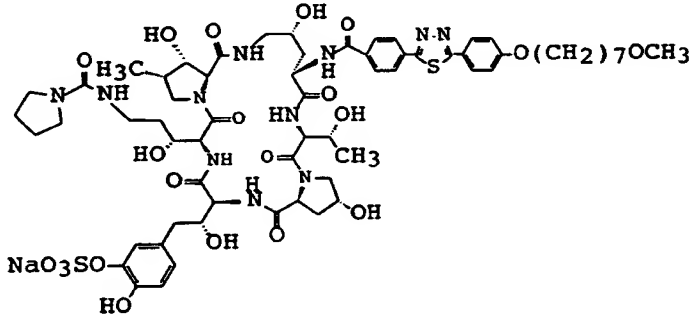
Example No.	Formula
41	
	
42	
	

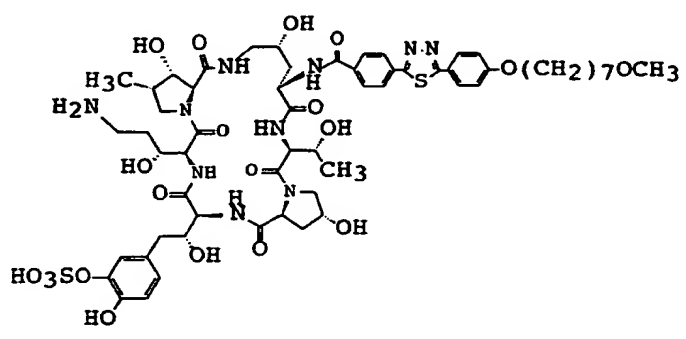
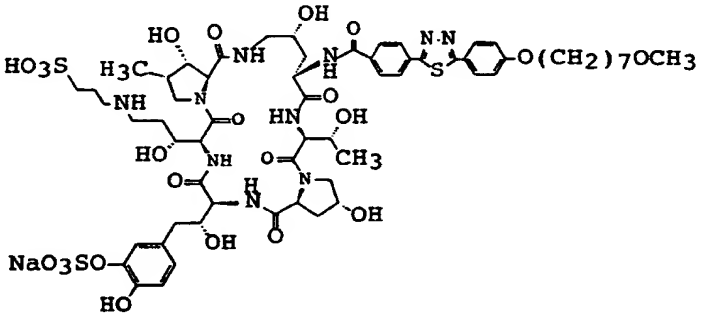
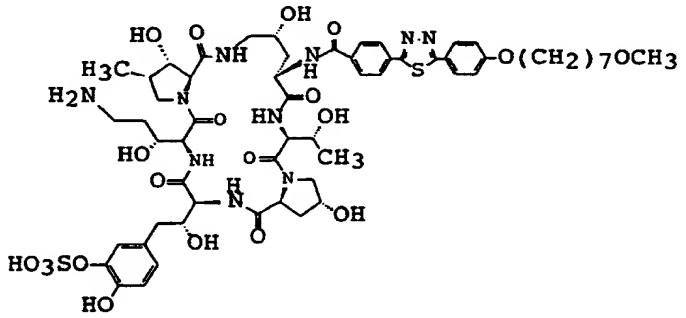
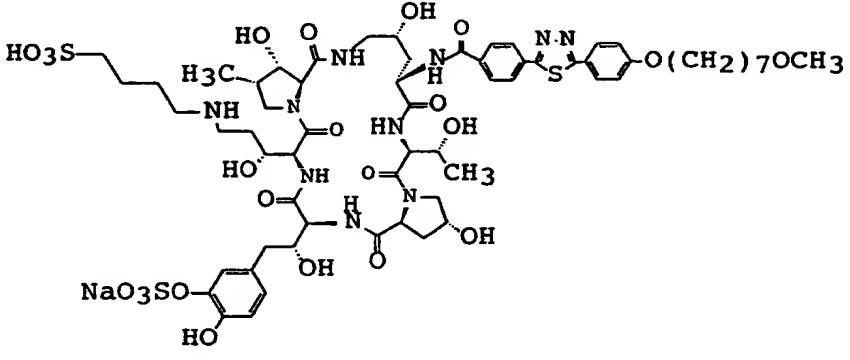
Example No.	Formula
43	 <p>Chemical structure of a complex molecule. It features a central core with multiple amide and ester linkages. A sulfonamide group is attached to one side, and a long alkoxy chain (O(CH₂)₇OCH₃) is attached to the other. The molecule also contains several hydroxyl groups and a methyl group.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a sodium sulfonate group (NaO₃SO) instead of a sulfonamide group.</p>
44	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different arrangement of the amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different arrangement of the amide and ester linkages.</p>

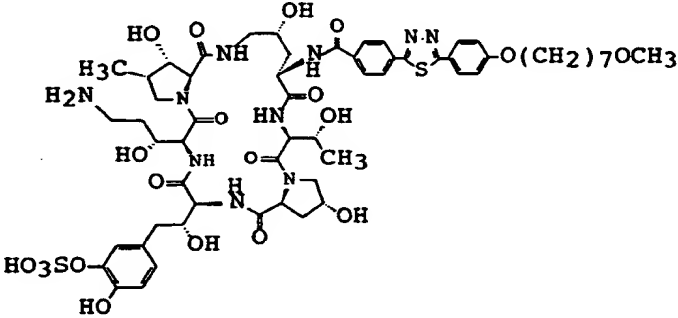
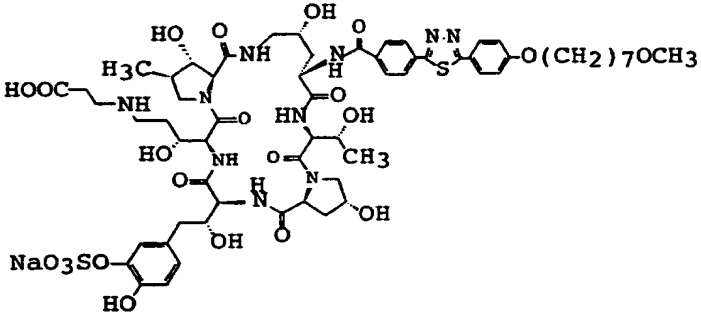
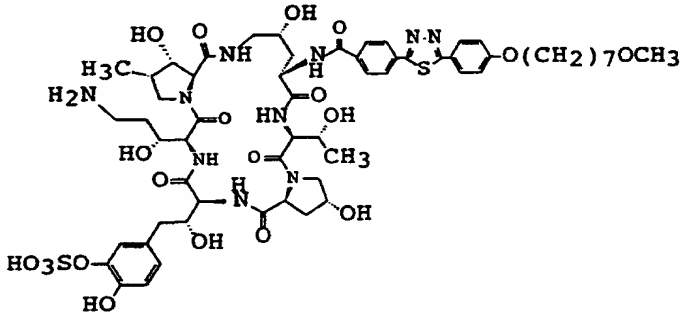
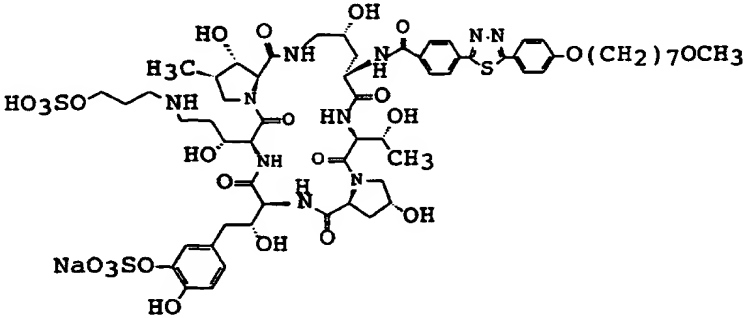
Example No.	Formula
45	
	

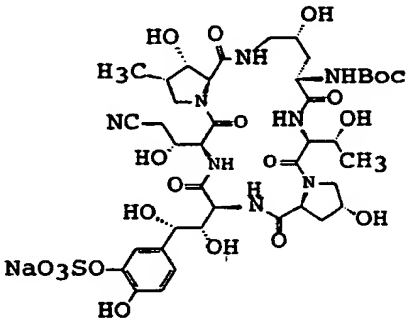
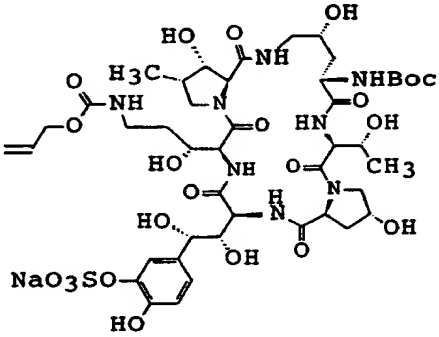
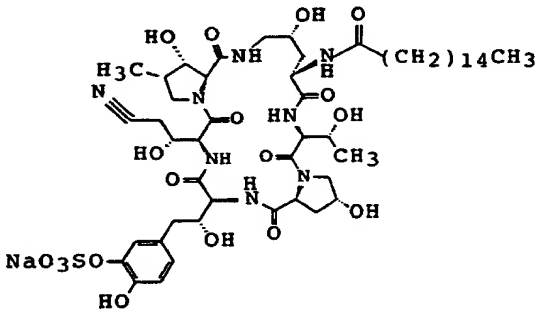
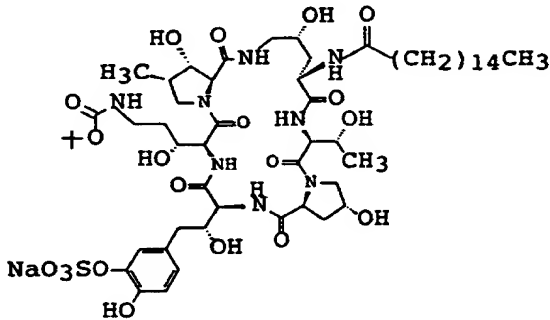
Example No.	Formula
46	
	

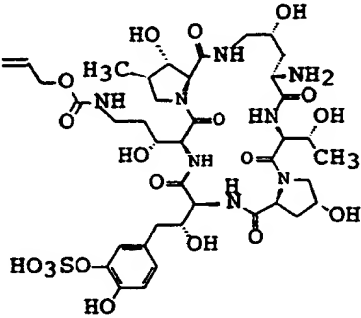
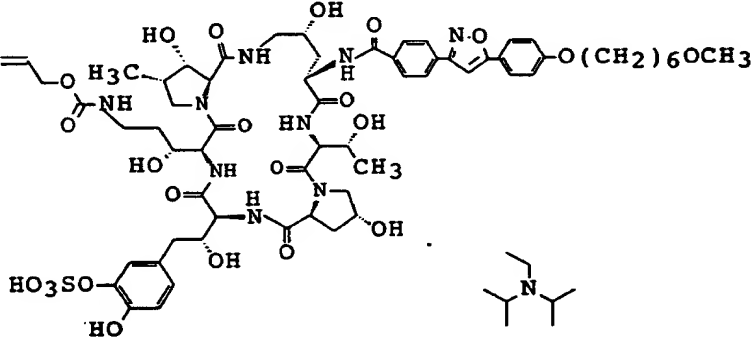
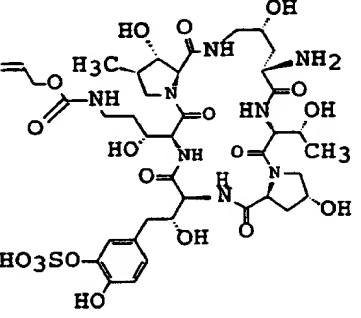
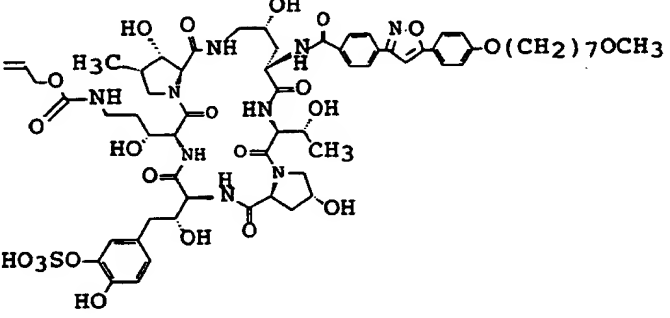
Example No.	Formula
47	deleted
	deleted
48	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO₃SO-). The structure is highly branched and includes a long chain ending in a methoxy group (O(CH₂)₇OCH₃).</p>
	 <p>Chemical structure of a complex molecule, similar to the one above but with a different sulfonate group (NaO₃SO-). It also features a central core with multiple hydroxyl groups, amide bonds, and a long chain ending in a methoxy group (O(CH₂)₇OCH₃).</p>

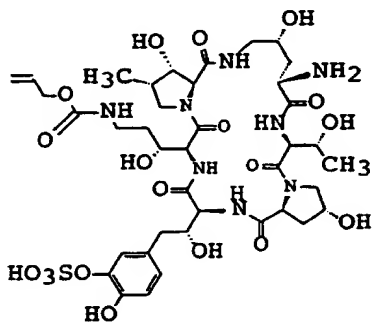
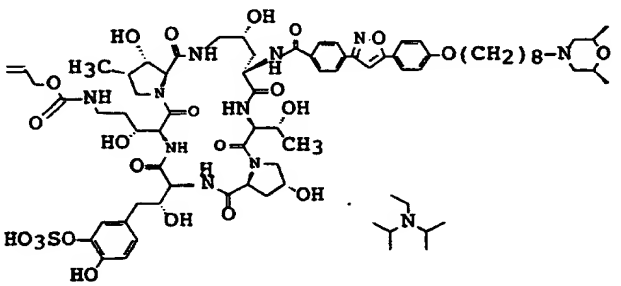
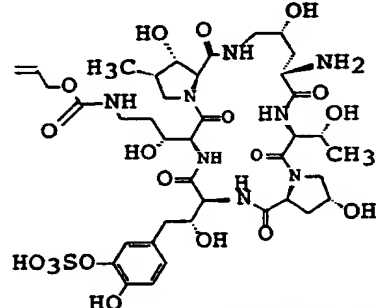
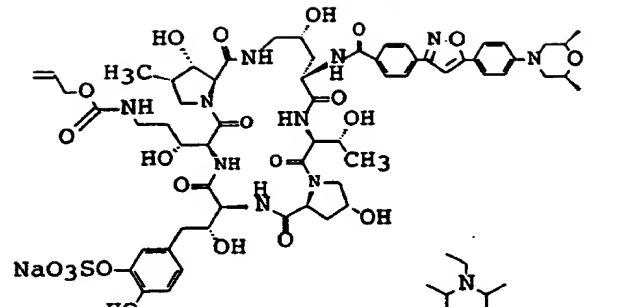
Example No.	Formula
51	
	
52	
	

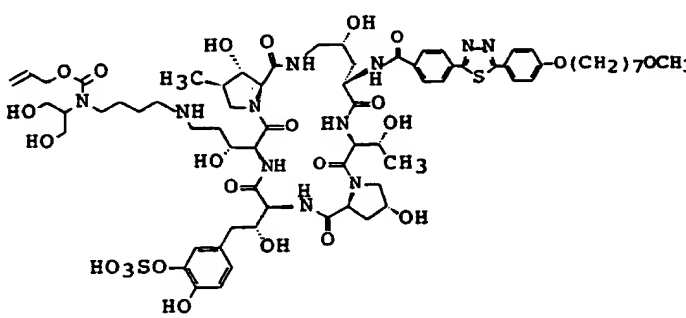
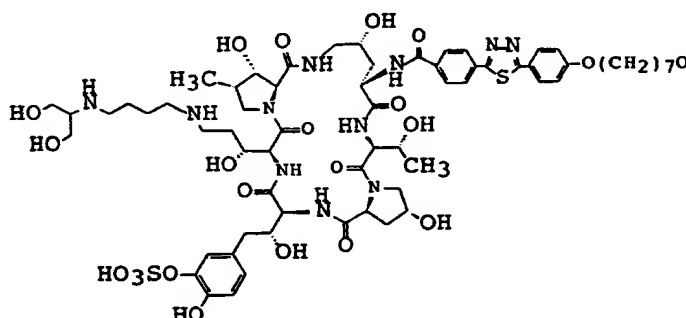
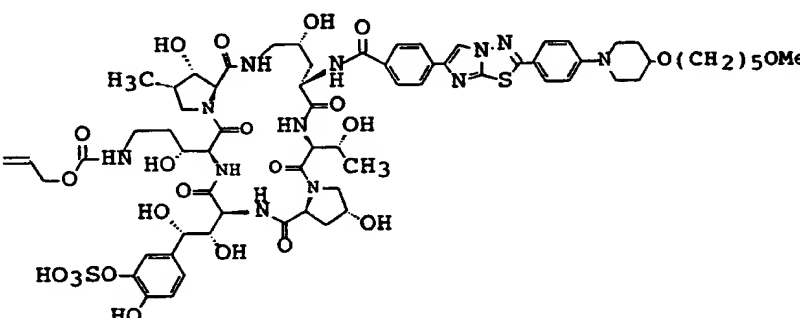
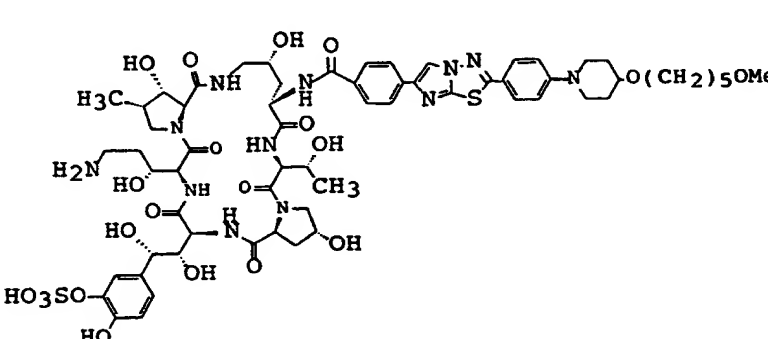
Example No.	Formula
53	
	
54	
	

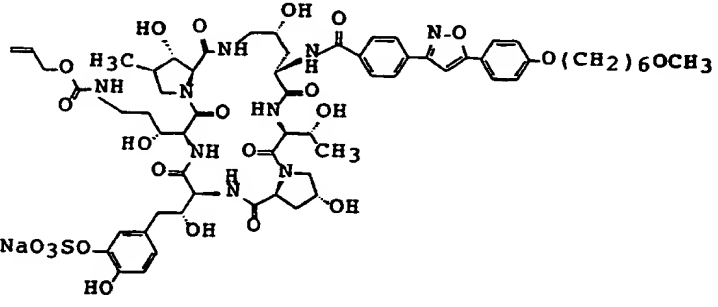
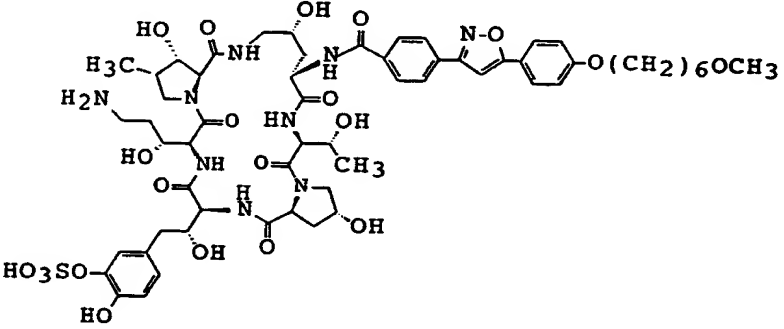
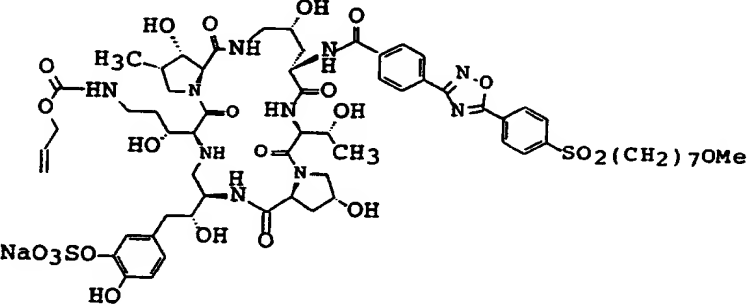
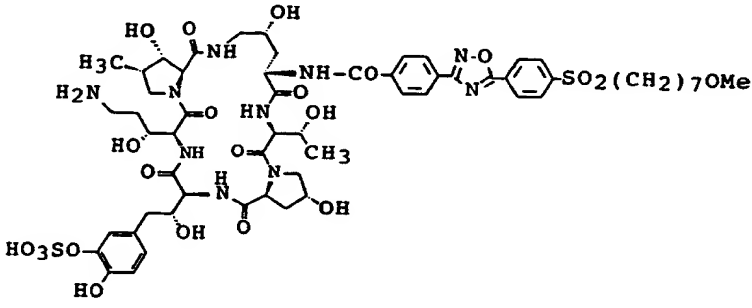
Example No.	Formula
55	
	
56	
	

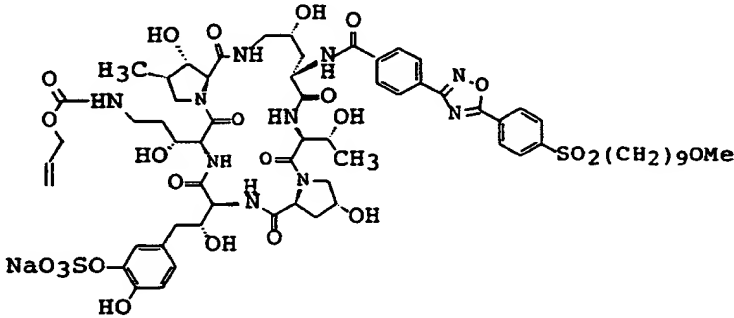
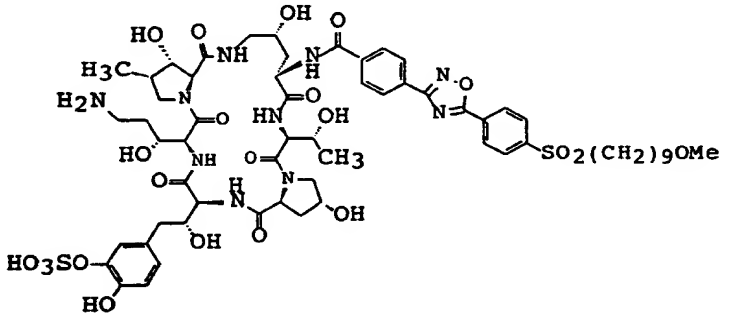
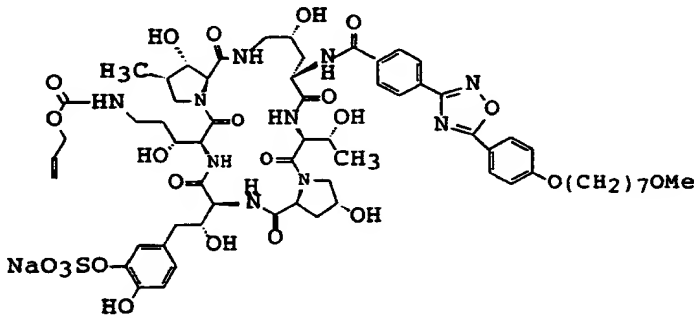
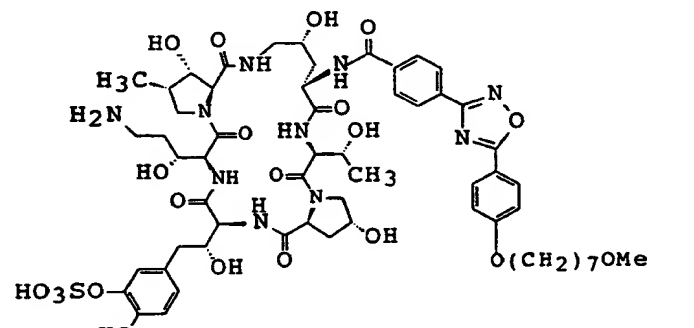
Example No.	Formula
57	
	
58	
	

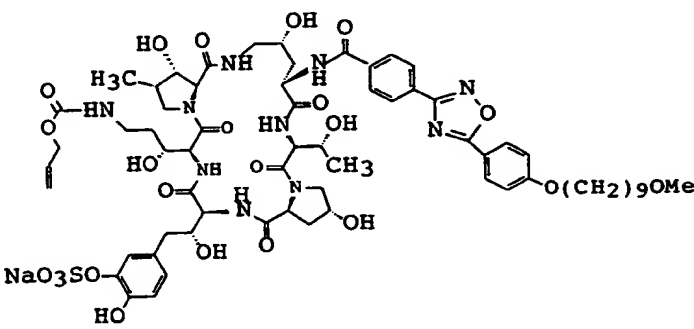
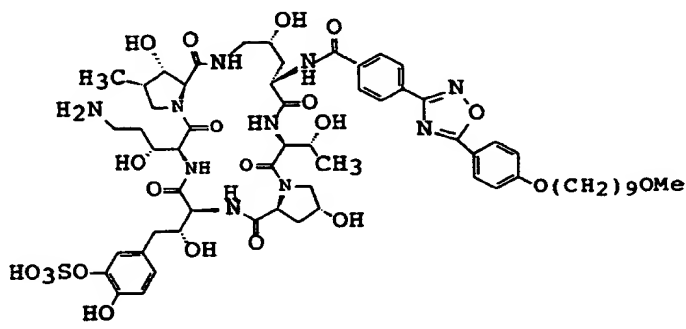
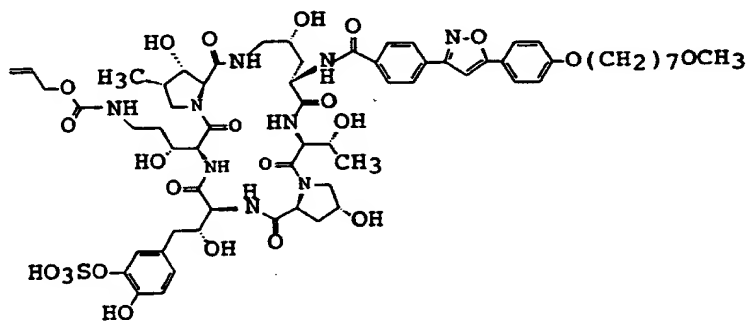
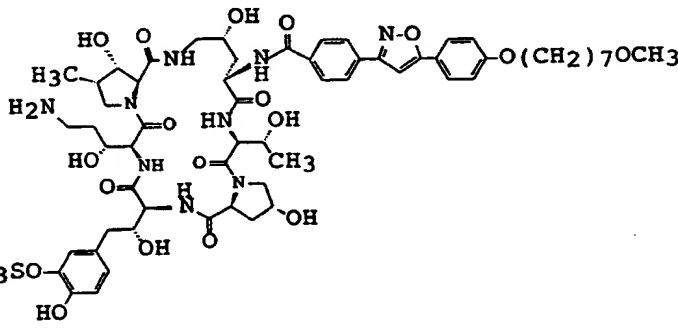
Example No.	Formula
59	
	
60	
	

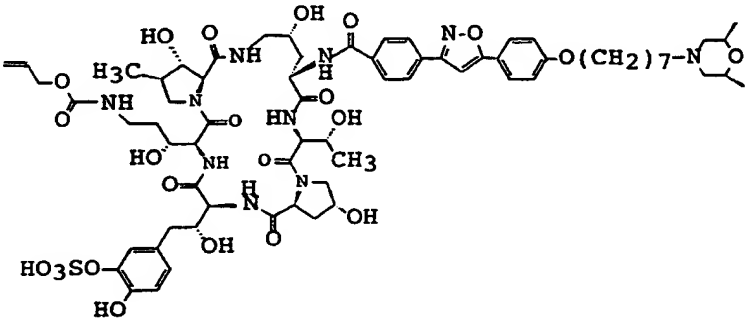
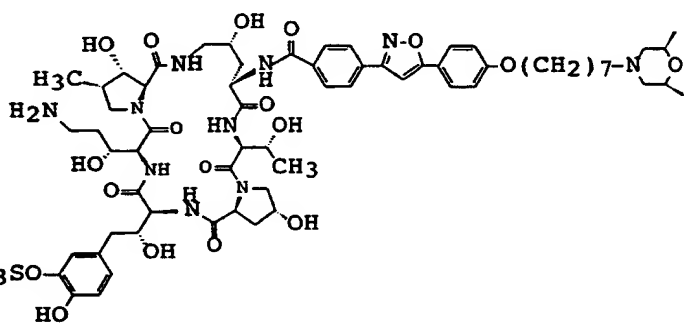
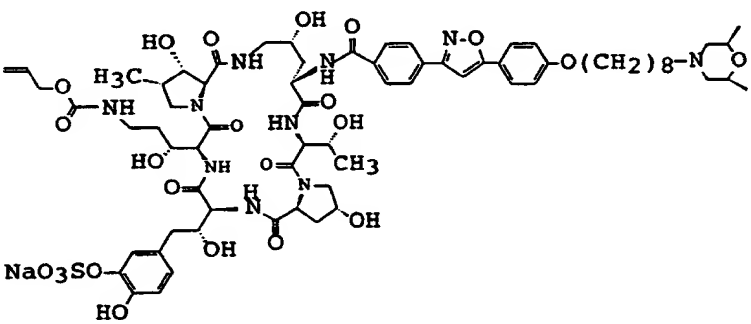
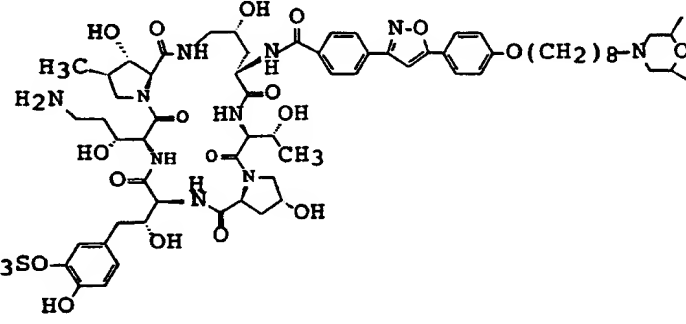
Example No.	Formula
61	 <p>Chemical structure of a complex molecule, likely a derivative of a natural product. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO₃SO-). The structure is highly branched and contains several chiral centers.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a long alkyl chain (CH₂)₈ attached to the sulfonate group. It also features a dimethylamino group (N(CH₃)₂) and a hydroxyl group.</p>
62	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different sulfonate group (NaO₃SO-). It also features a dimethylamino group (N(CH₃)₂) and a hydroxyl group.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a long alkyl chain (CH₂)₈ attached to the sulfonate group. It also features a dimethylamino group (N(CH₃)₂) and a hydroxyl group.</p>

Example No.	Formula
63	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a sulfonate group (HO₃SO-), and a long alkoxy chain (O(CH₂)₇OCH₃). The structure is highly branched and includes several amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above but with a different alkoxy chain (O(CH₂)₇OCH₃). It features a central core with multiple hydroxyl groups, a sulfonate group (HO₃SO-), and a long alkoxy chain.</p>
64	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a sulfonate group (HO₃SO-), and a long alkoxy chain (O(CH₂)₅OMe). The structure is highly branched and includes several amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above but with a different alkoxy chain (O(CH₂)₅OMe). It features a central core with multiple hydroxyl groups, a sulfonate group (HO₃SO-), and a long alkoxy chain.</p>

Example No.	Formula
65	
	
66	
	

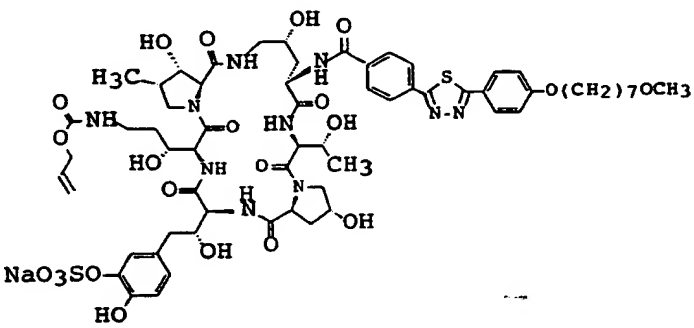
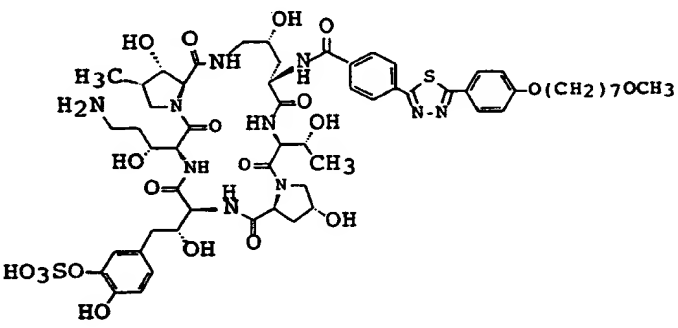
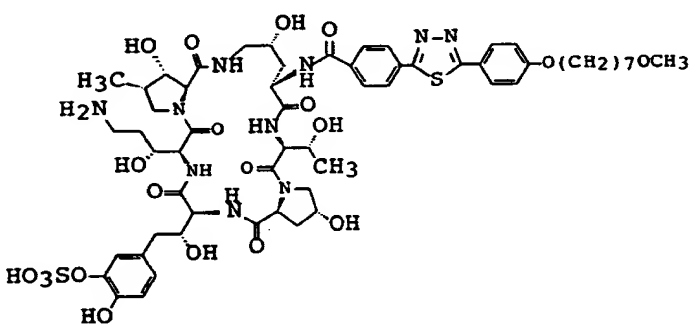
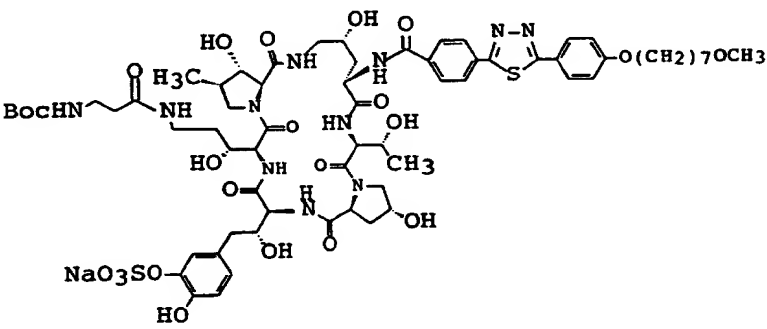
Example No.	Formula
67	
	
68	
	

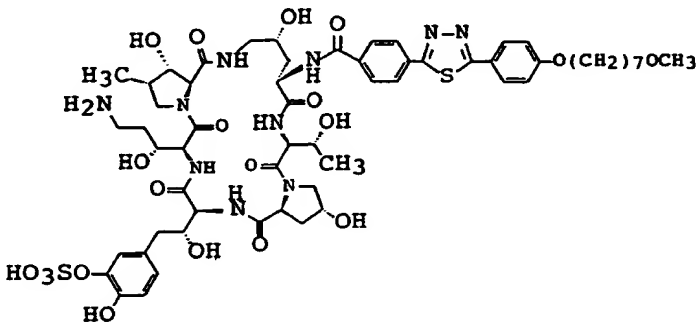
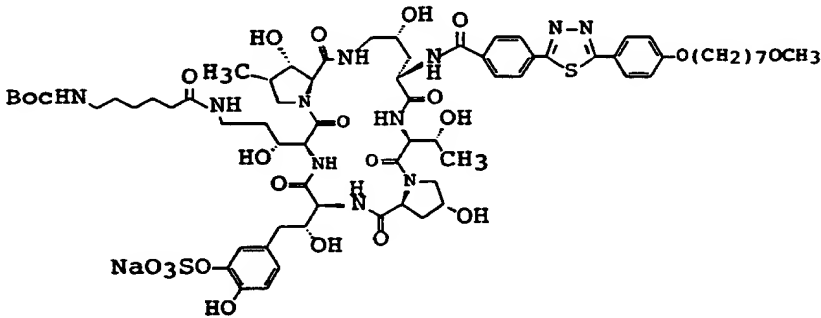
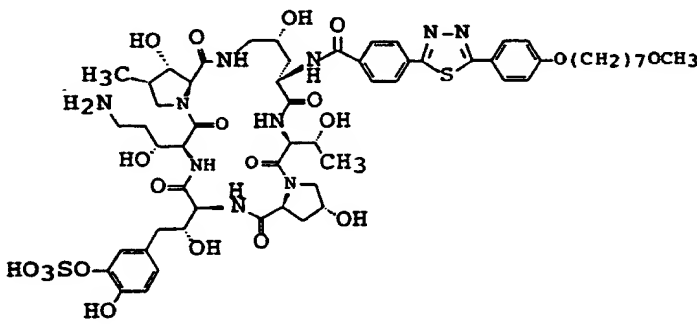
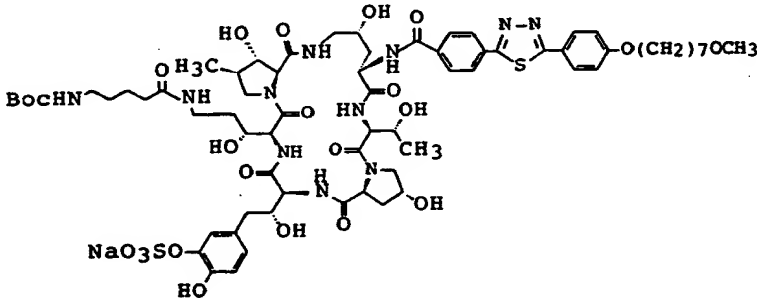
Example No.	Formula
69	
	
70	
	

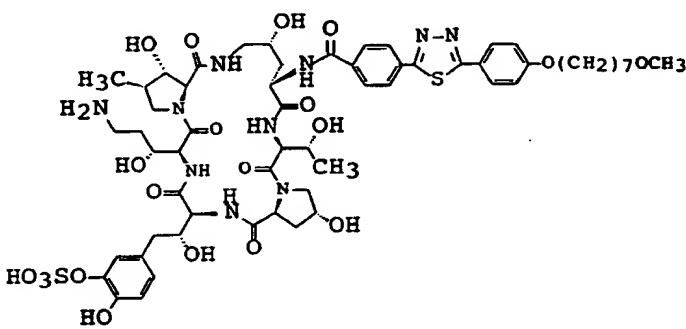
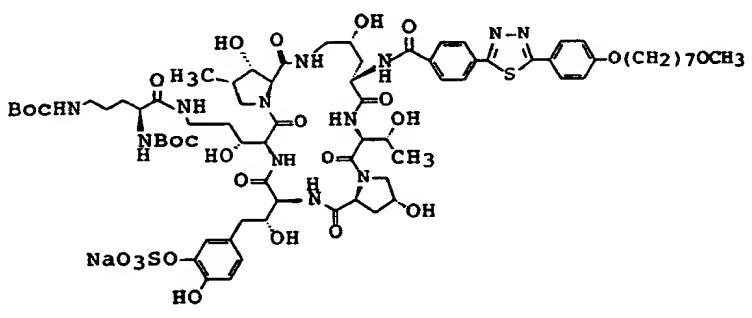
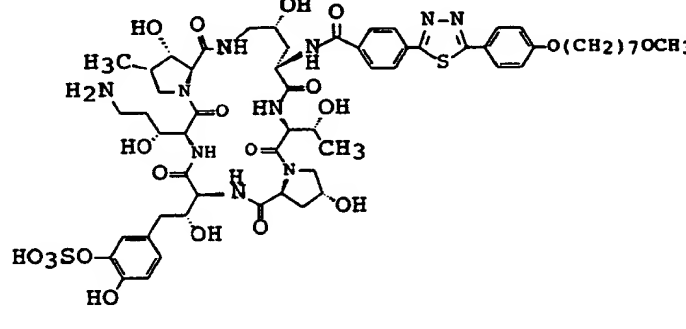
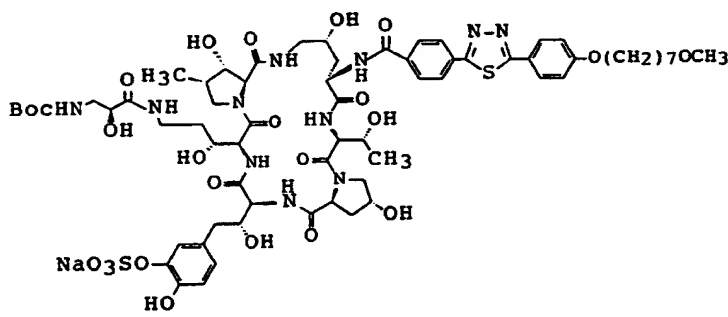
Example No.	Formula
71	
	
72	
	

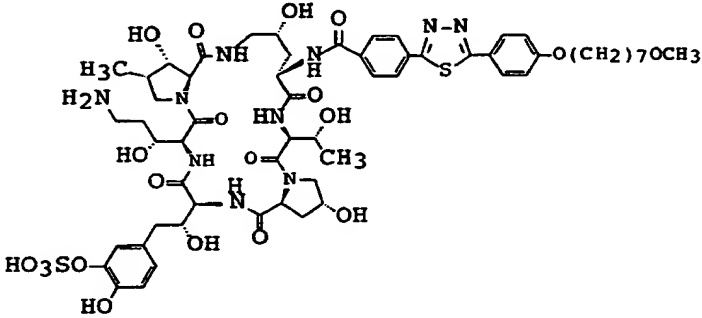
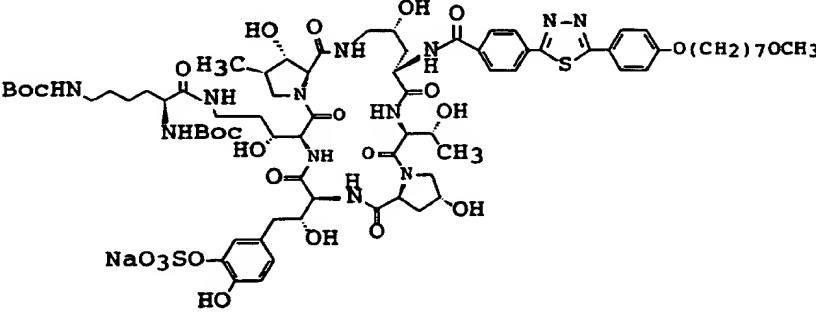
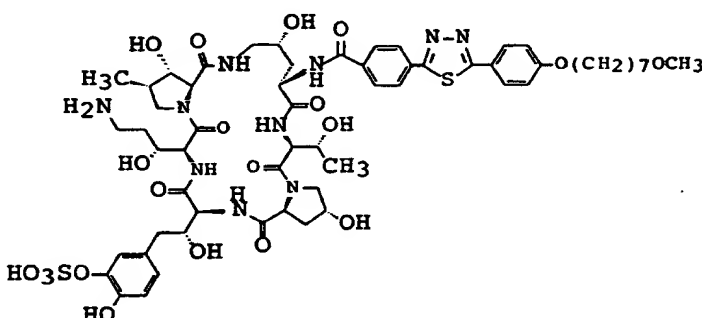
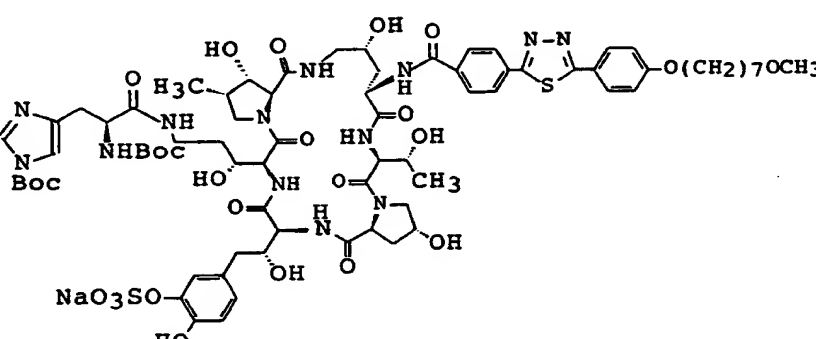
Example No.	Formula
73	
74	

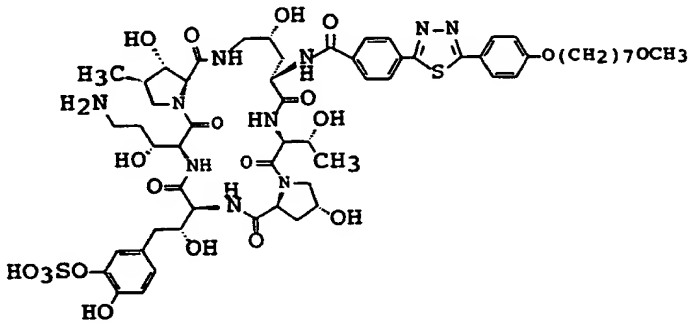
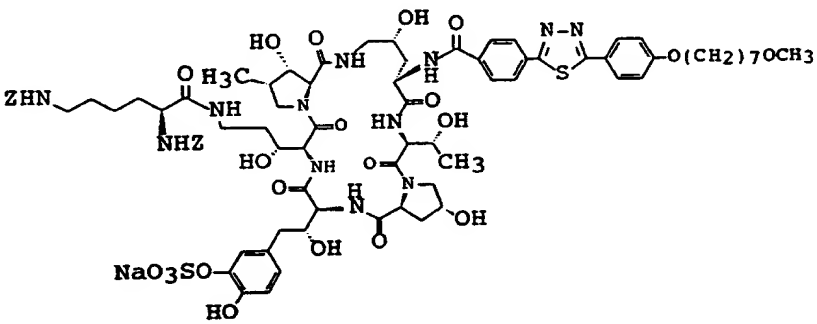
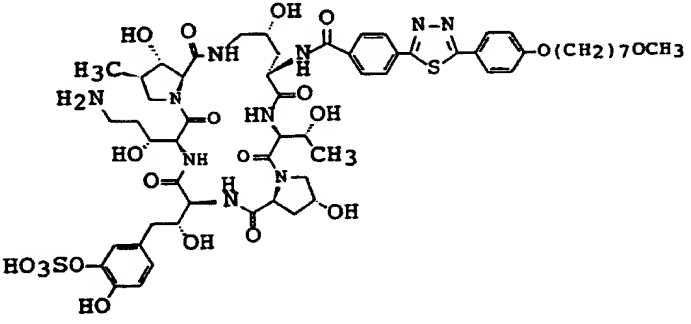
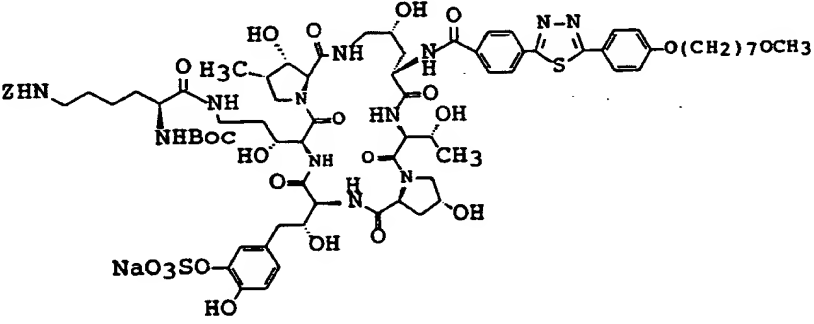
Example No.	Formula
75	
76	

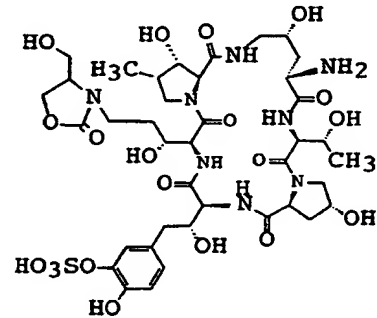
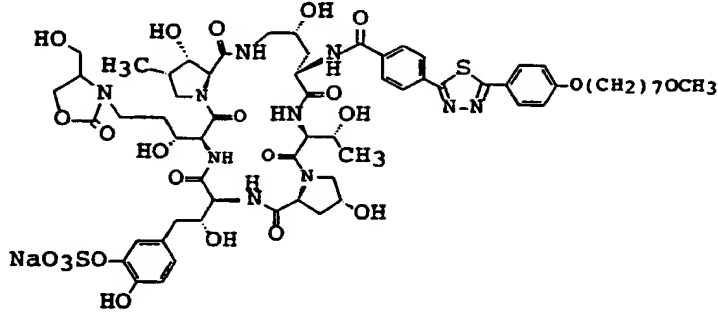
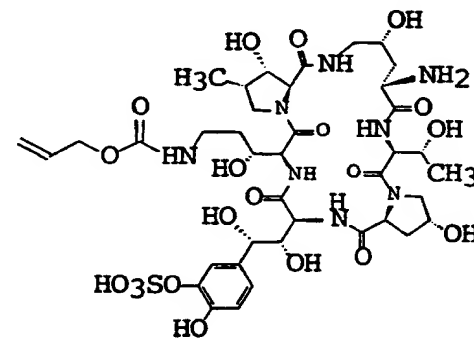
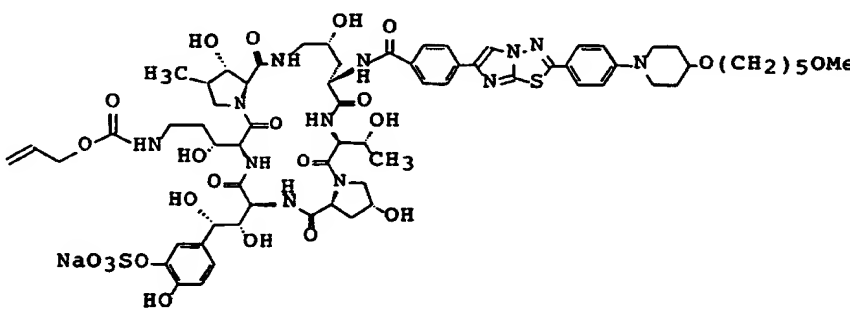
Example No.	Formula
77	
	
78	
	

Example No.	Formula
79	
	
80	
	

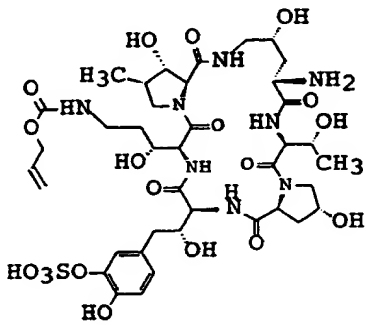
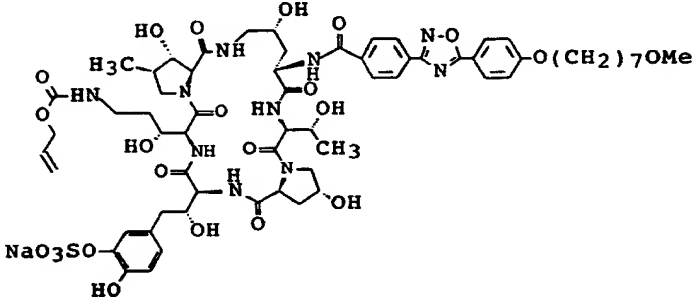
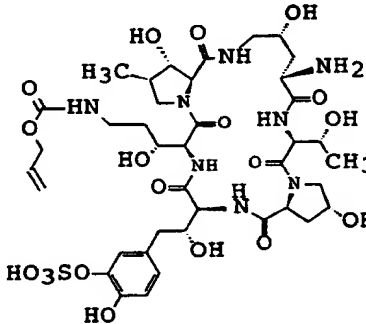
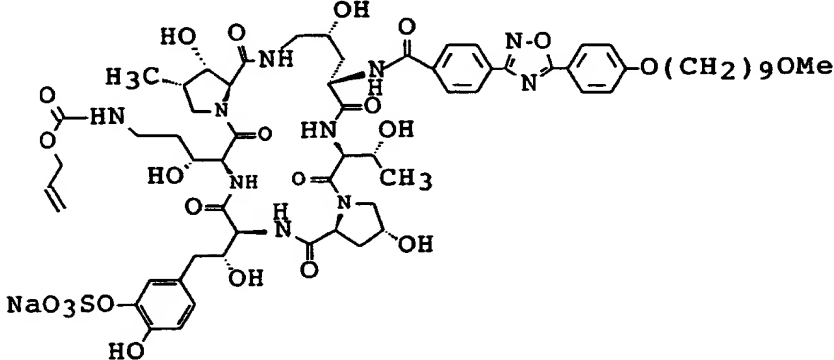
Example No.	Formula
81	
	
82	
	

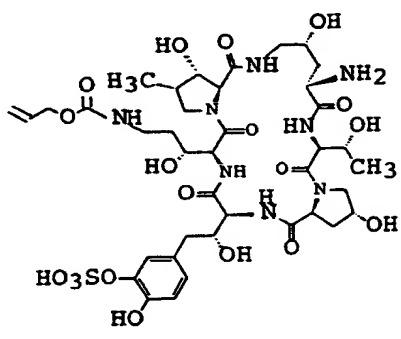
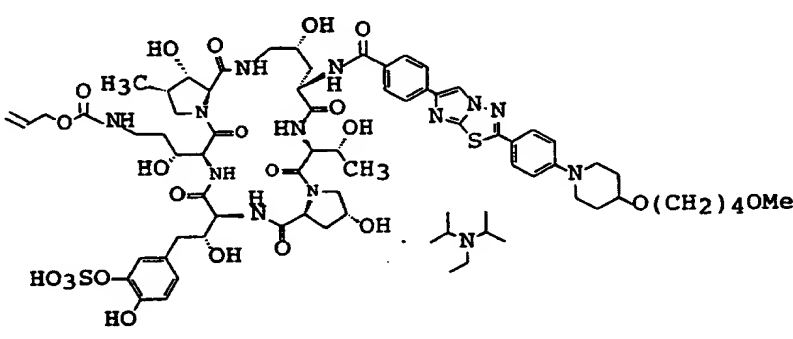
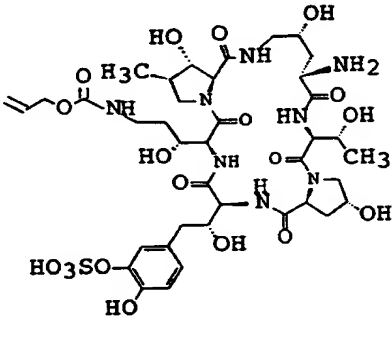
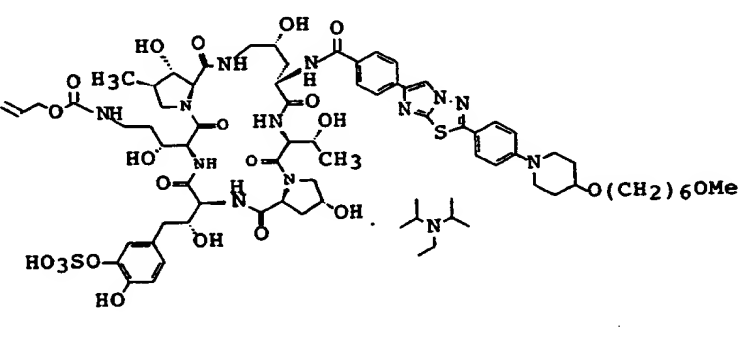
Example No.	Formula
83	
	
84	
	

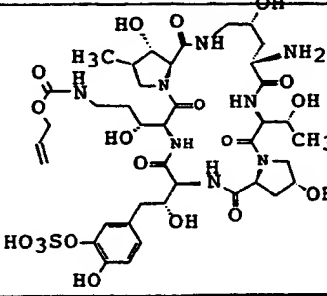
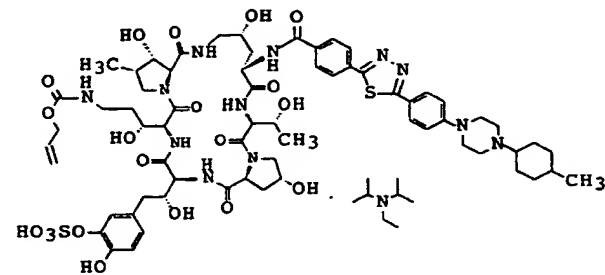
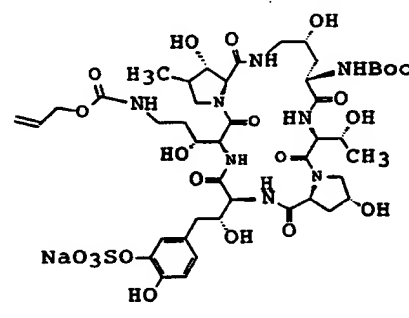
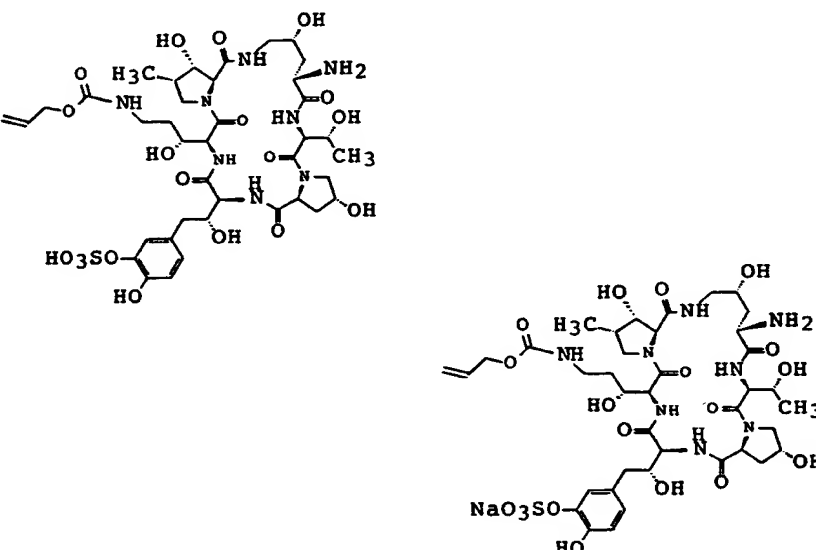
Example No.	Formula
85	
	
86	
	

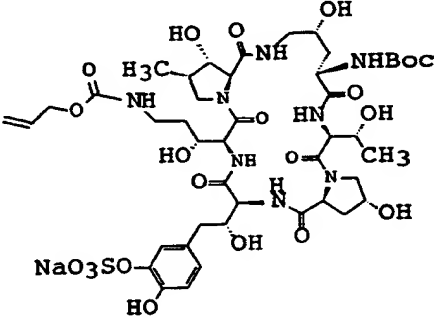
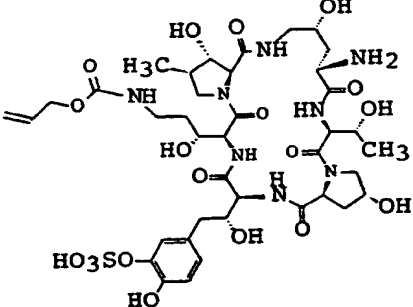
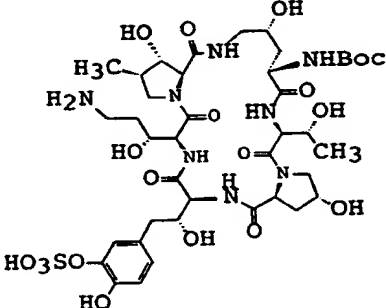
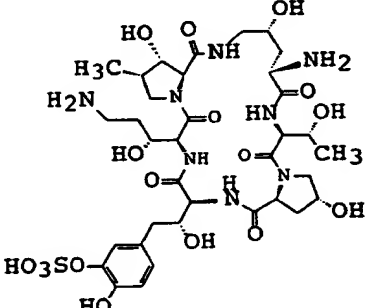
Example No.	Formula
87	
	
88	
	

Example No.	Formula
89	
90	

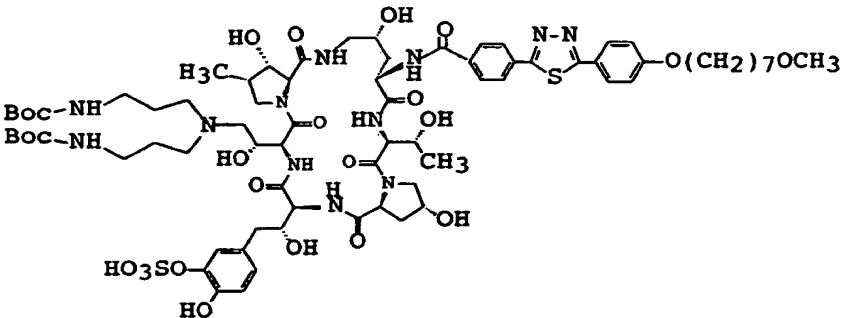
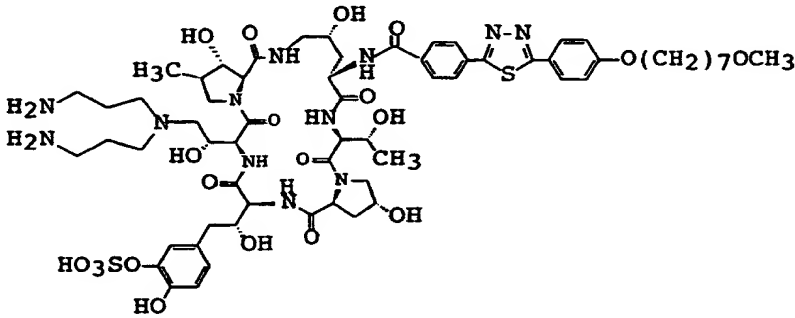
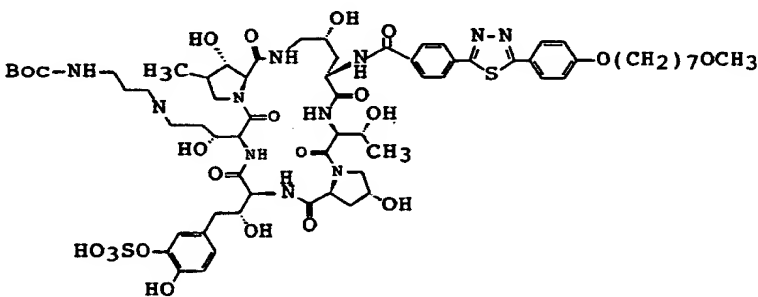
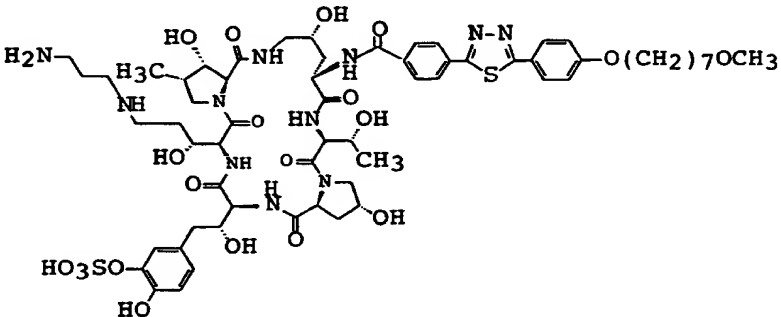
Example No.	Formula
91	
	
92	
	

Example No.	Formula
93	 <p>Chemical structure of Example 93, top formula. It is a complex molecule featuring a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO₃SO) attached to a phenyl ring. The structure includes a vinyl group and a methyl group.</p>
	 <p>Chemical structure of Example 93, bottom formula. This structure is similar to the top formula but includes a long chain containing a triazole ring system and a methoxy group (O(CH₂)₄OMe) at the end. It also features a dimethylamino group (N(CH₃)₂).</p>
94	 <p>Chemical structure of Example 94, top formula. It is a complex molecule featuring a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO₃SO) attached to a phenyl ring. The structure includes a vinyl group and a methyl group.</p>
	 <p>Chemical structure of Example 94, bottom formula. This structure is similar to the top formula but includes a long chain containing a triazole ring system and a methoxy group (O(CH₂)₆OMe) at the end. It also features a dimethylamino group (N(CH₃)₂).</p>

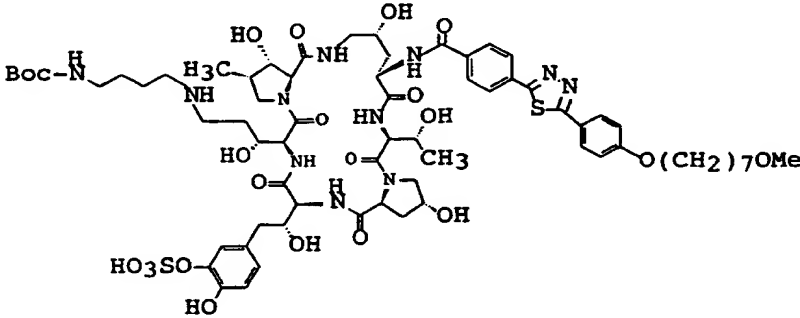
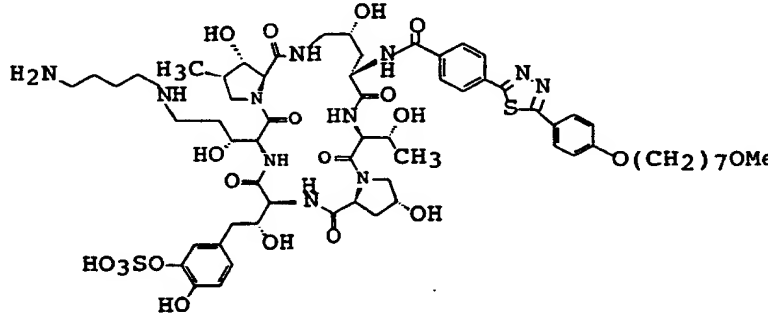
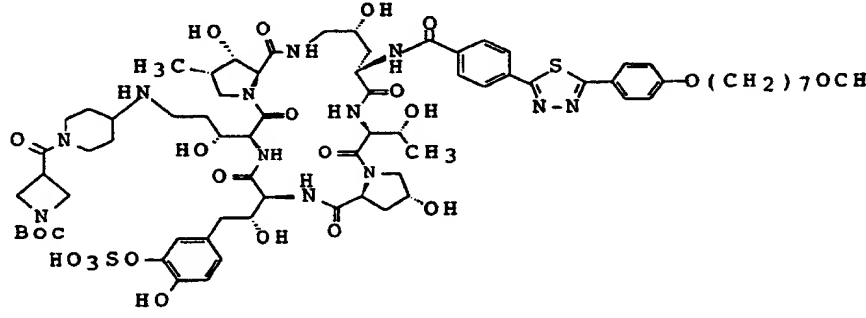
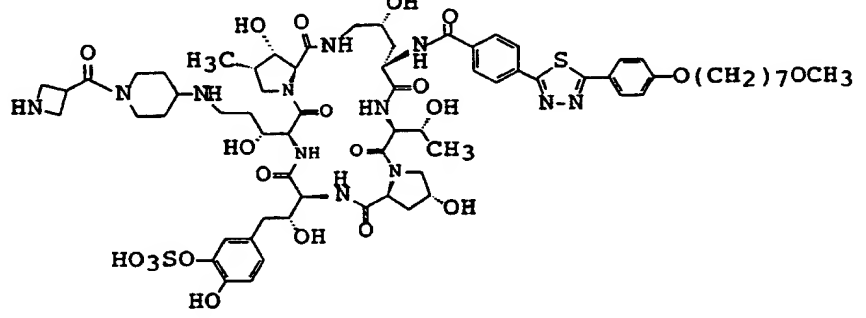
Example No.	Formula
95	
	
96	
	

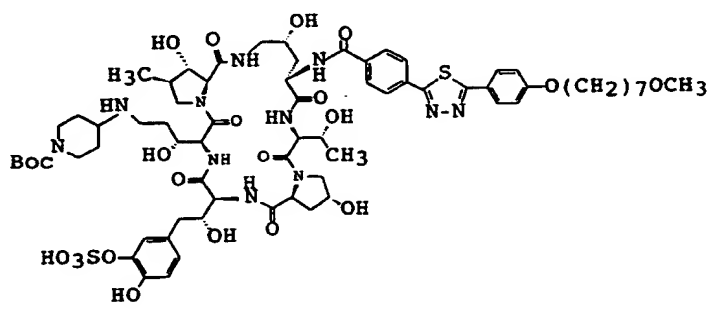
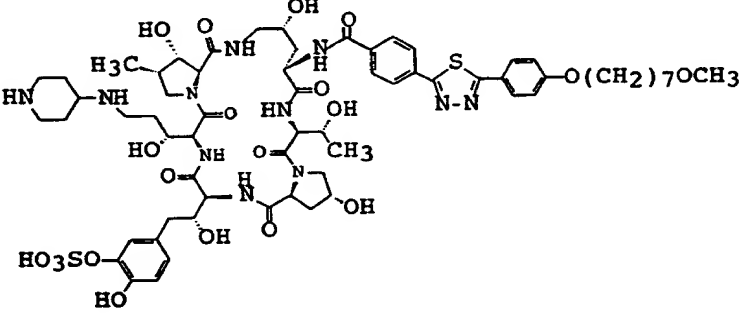
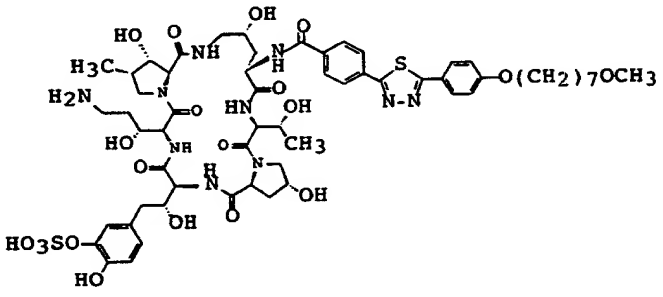
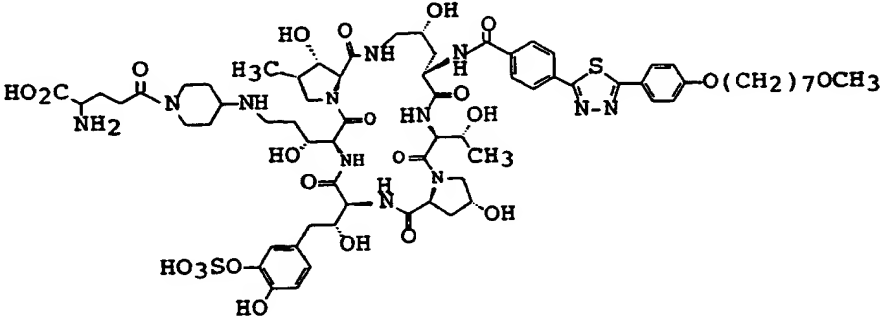
Example No.	Formula
97	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group (NaO₃SO-) attached to a phenyl ring. The molecule also contains a Boc-protected amine and a vinyl ether group.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a sulfonic acid group (HO₃SO-) instead of the sodium sulfonate group.</p>
98	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different substitution pattern on the phenyl ring, including a sulfonic acid group (HO₃SO-).</p>
	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different substitution pattern on the phenyl ring, including a sulfonic acid group (HO₃SO-).</p>

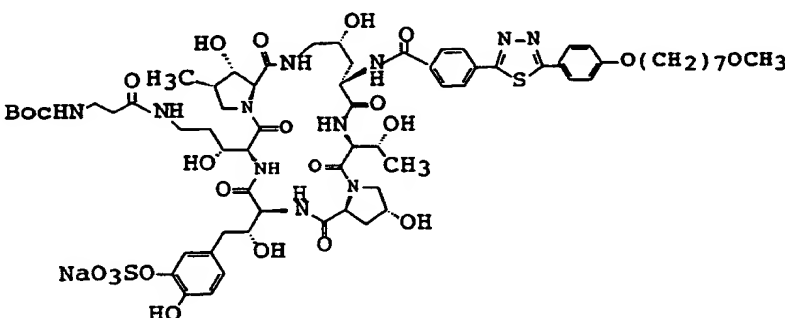
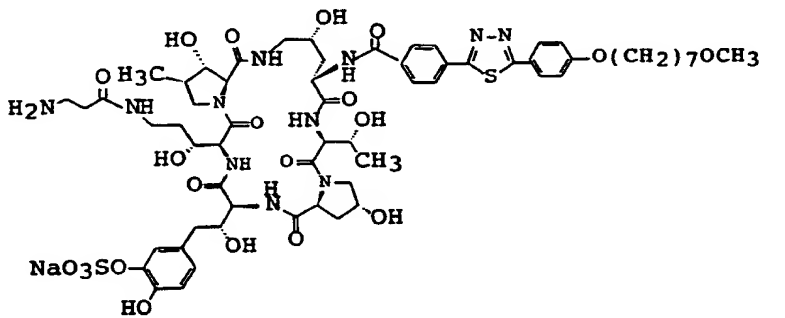
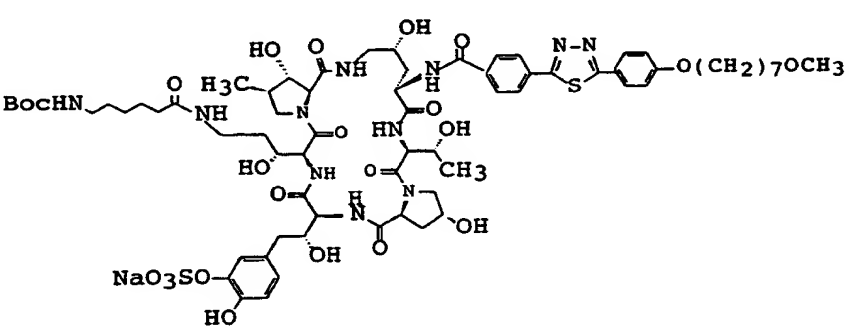
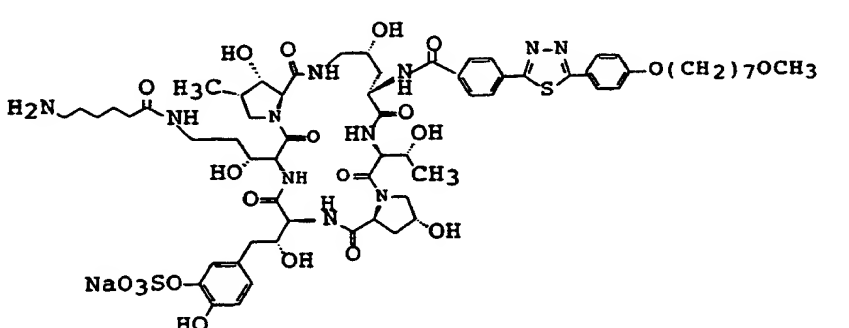
Example No.	Formula
99	
100	

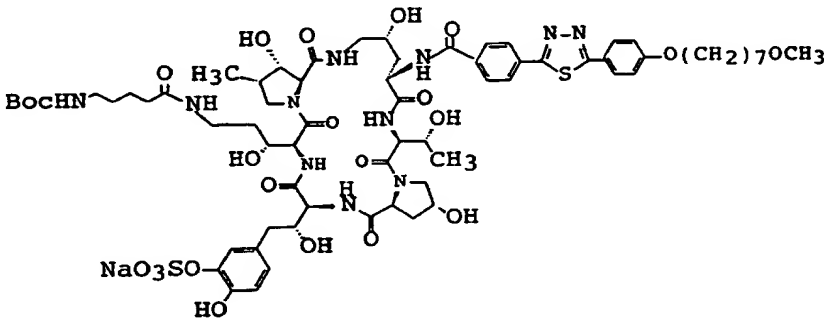
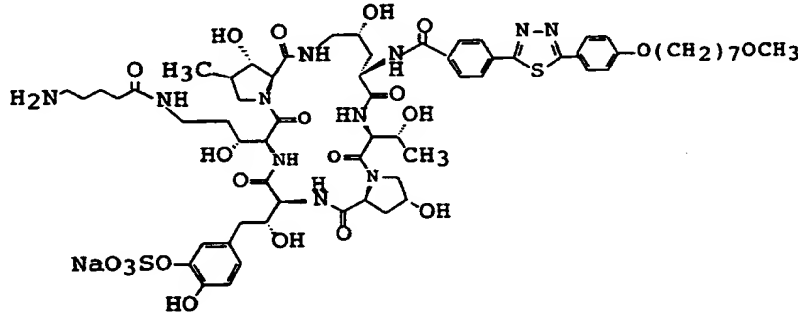
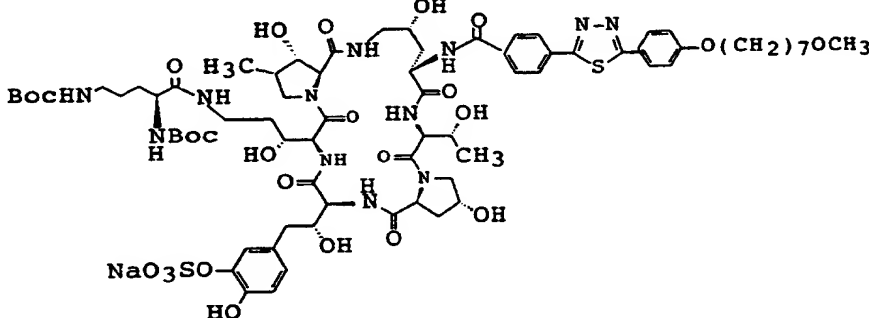
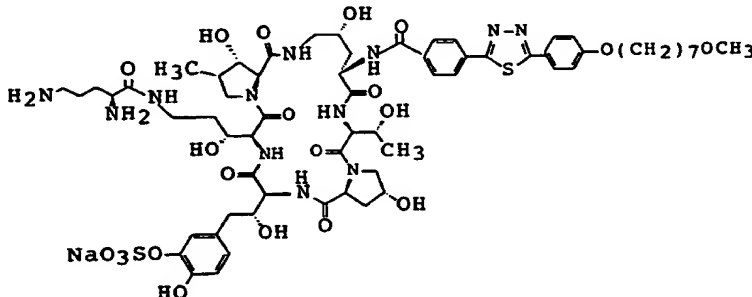
Example No.	Formula
101	
	
102	
	

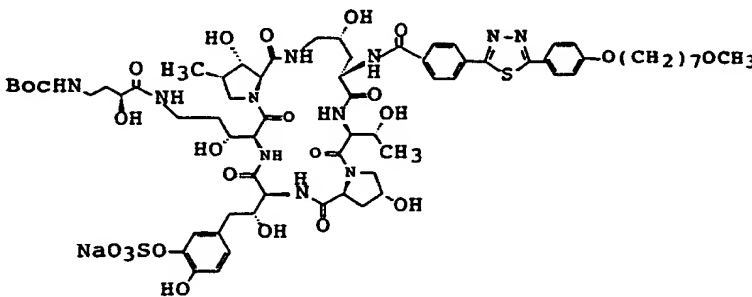
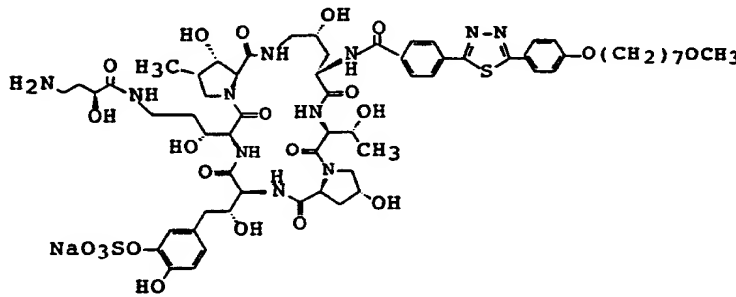
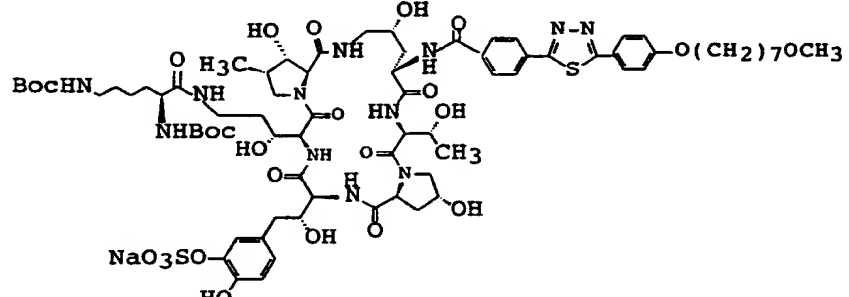
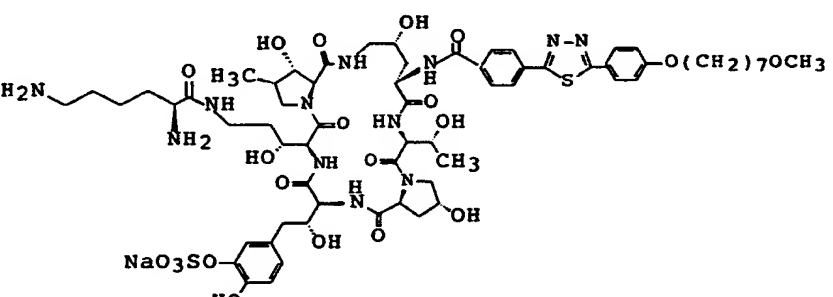
Example No.	Formula
103	
104	

Example No.	Formula
105	
	
106	
	

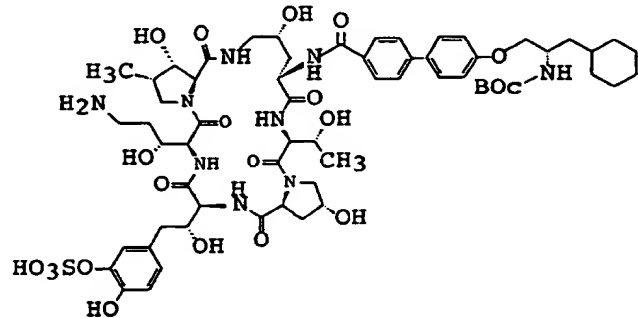
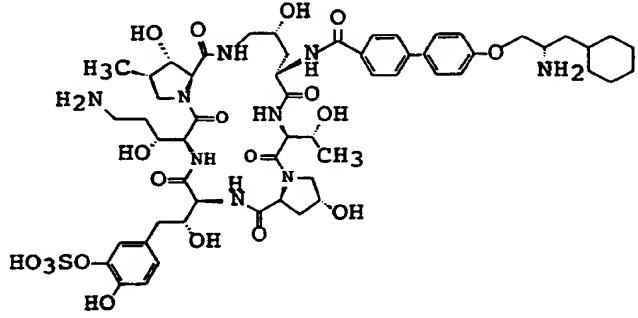
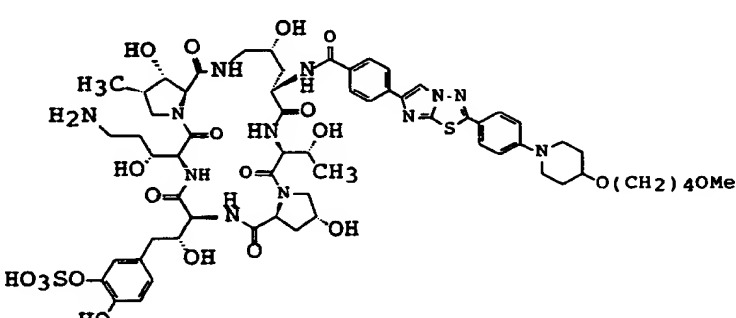
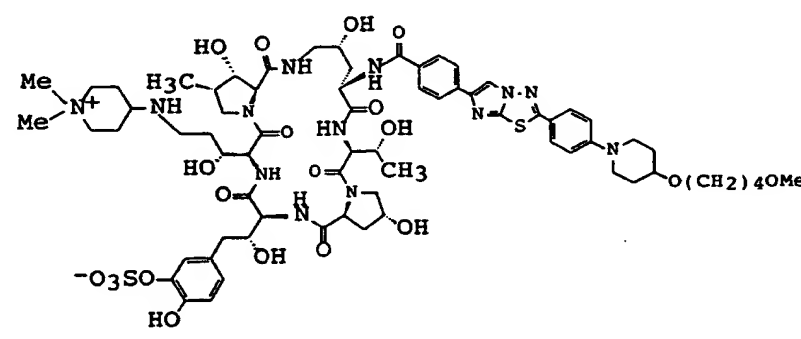
Example No.	Formula
107	
	
108	
	

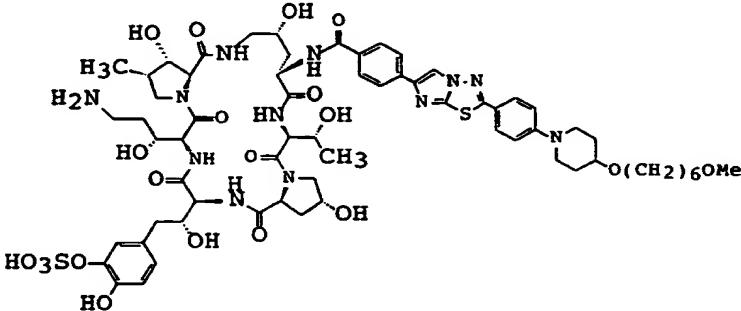
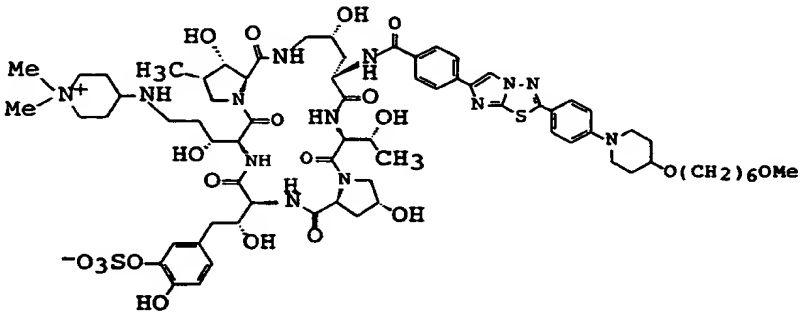
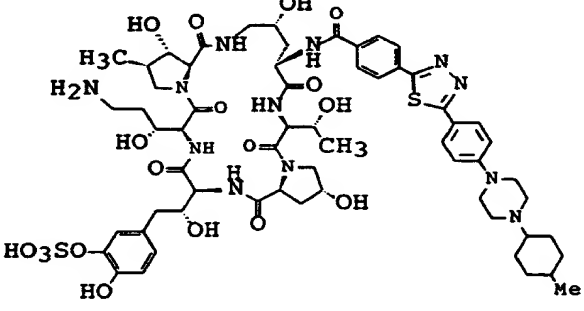
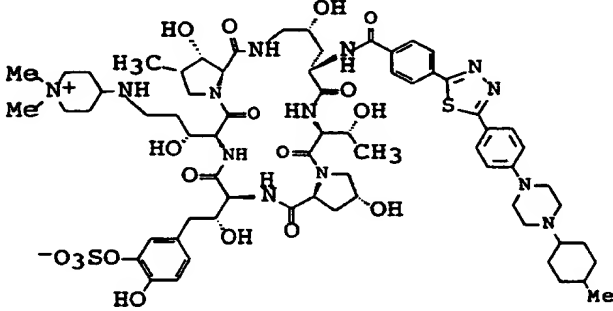
Example No.	Formula
109	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group. A long alkyl chain is attached to the structure, and a Boc-protected amine is present.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different substituent on the amine group.</p>
110	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different substituent on the amine group.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different substituent on the amine group.</p>

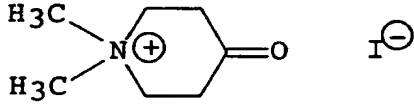
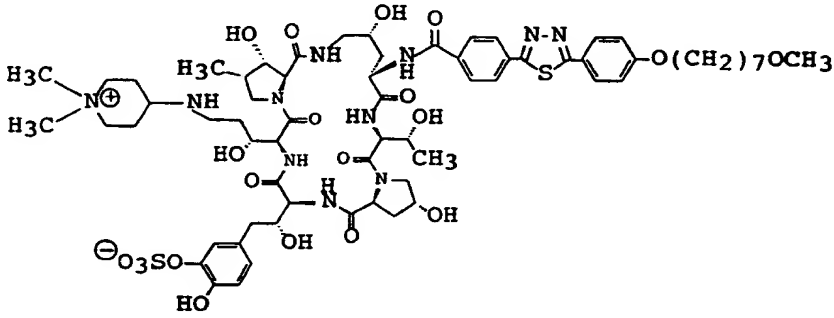
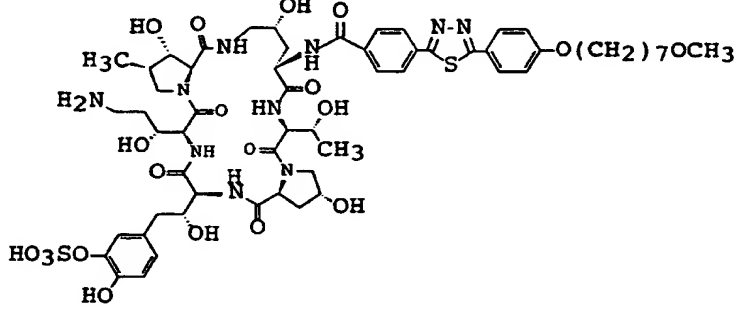
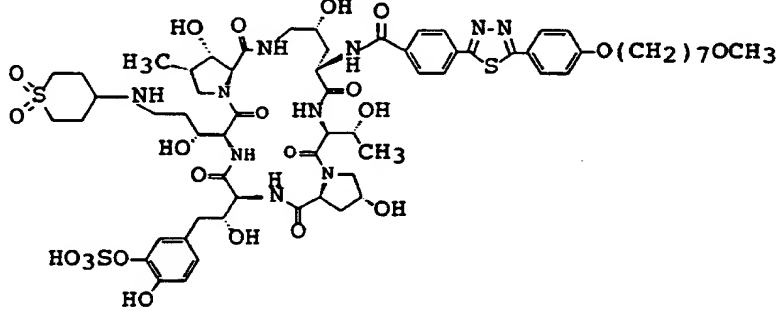
Example No.	Formula
111	
	
112	
	

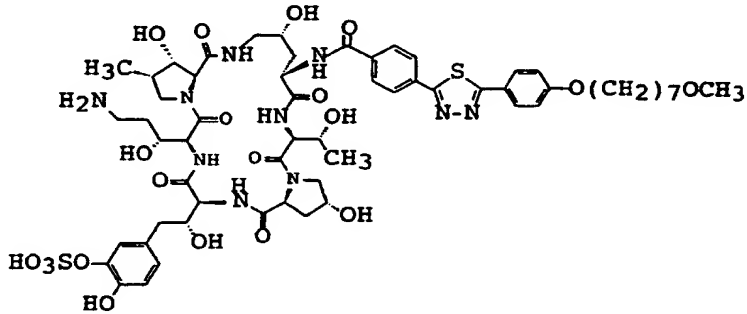
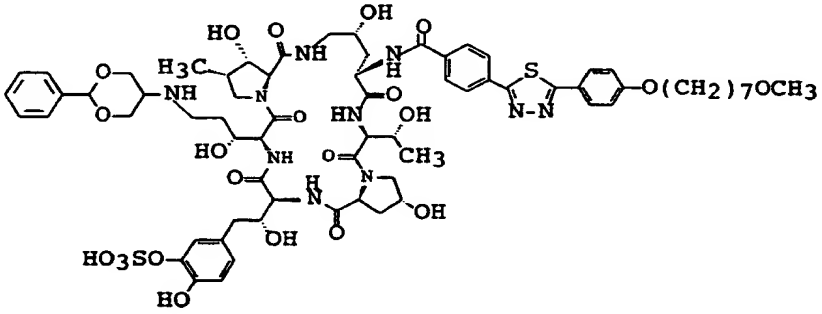
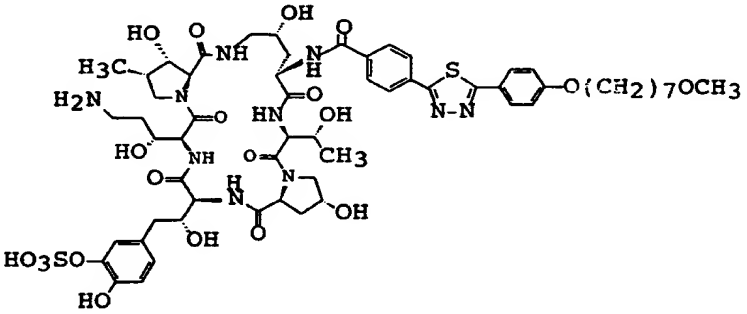
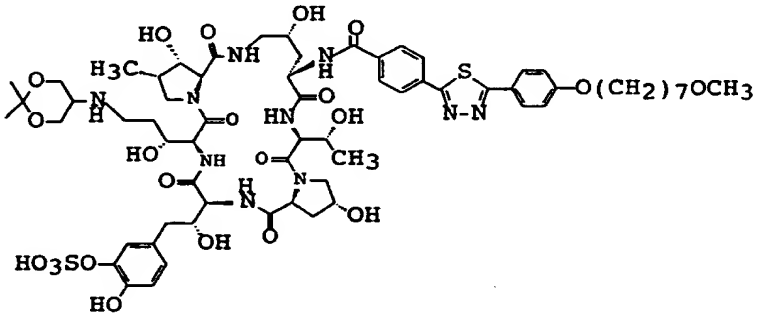
Example No.	Formula
113	
	
114	
	

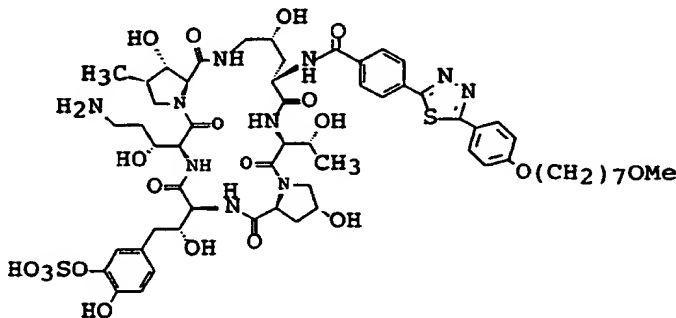
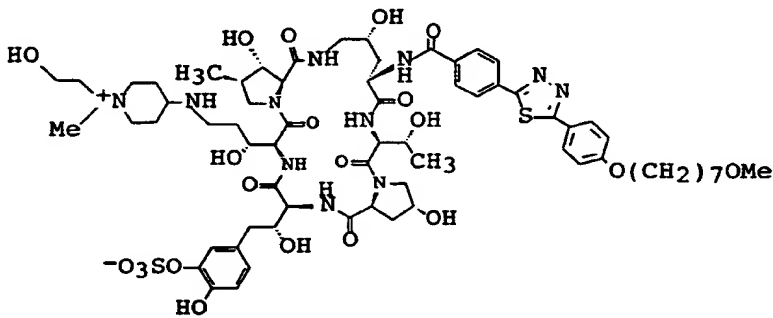
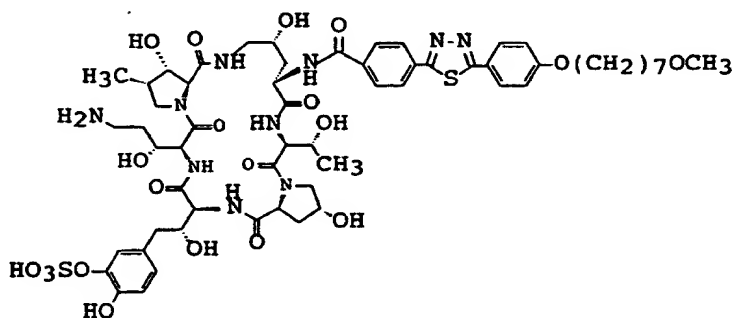
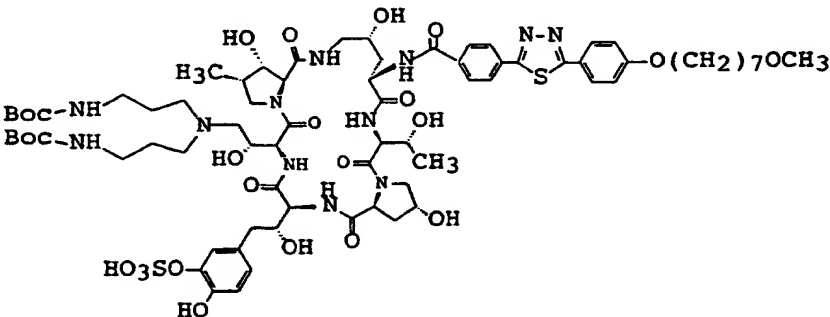
Example No.	Formula
115	
116	

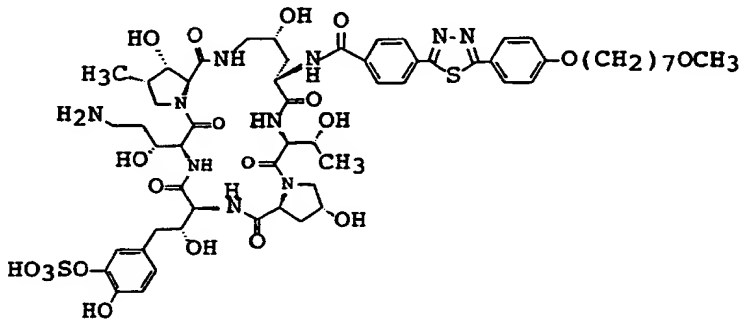
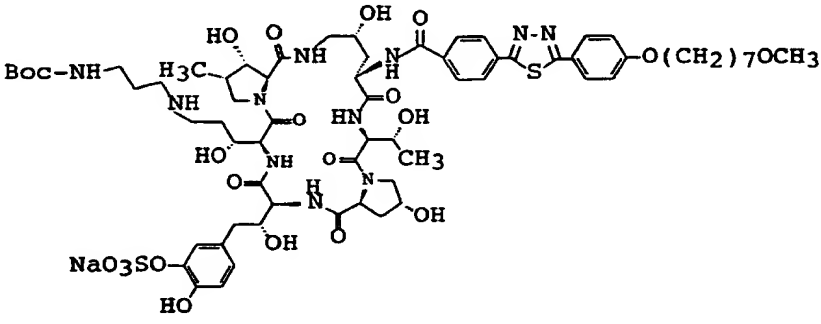
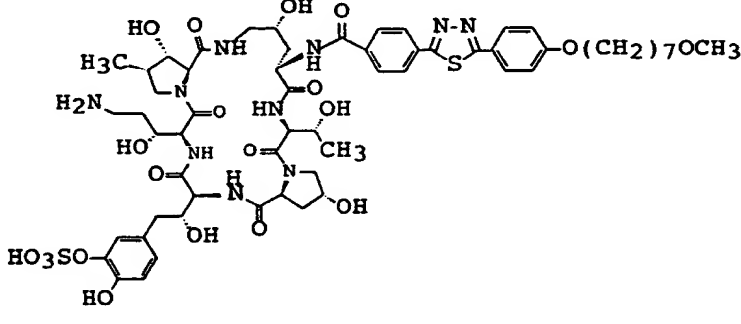
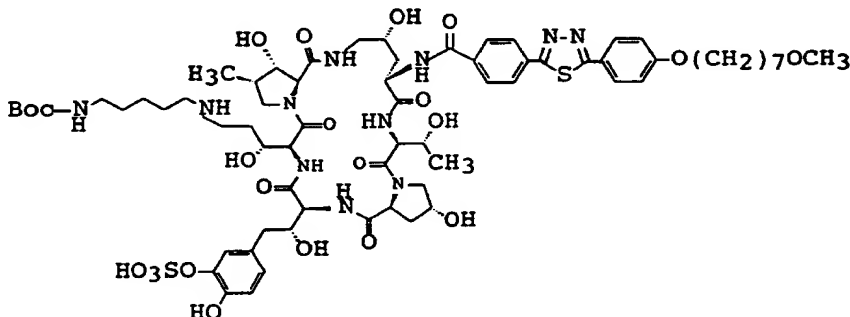
Example No.	Formula
117	
	
118	
	

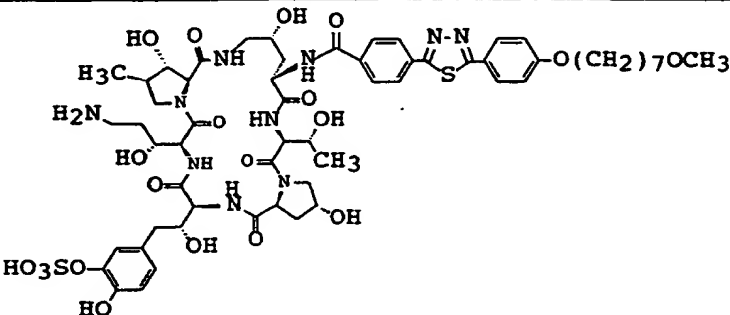
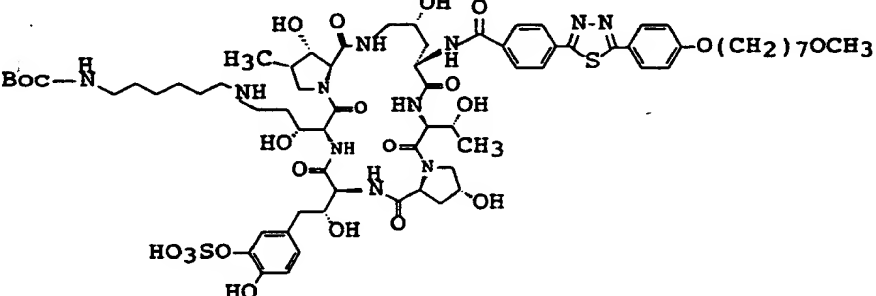
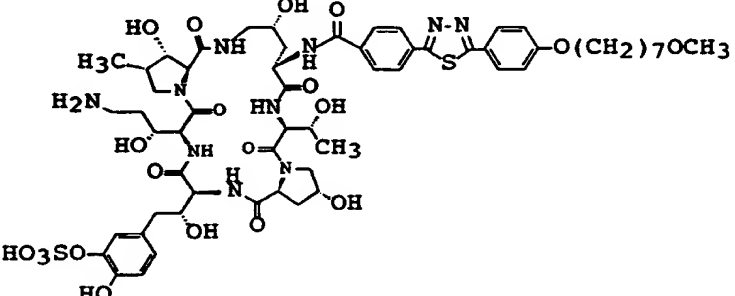
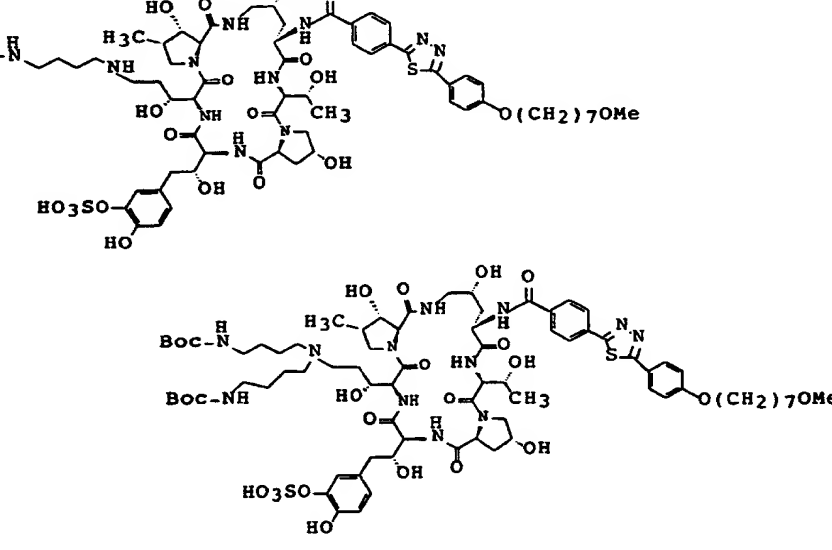
Example No.	Formula
119	
	
120	
	

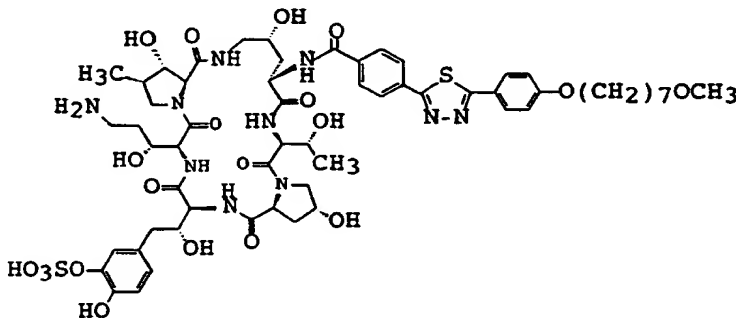
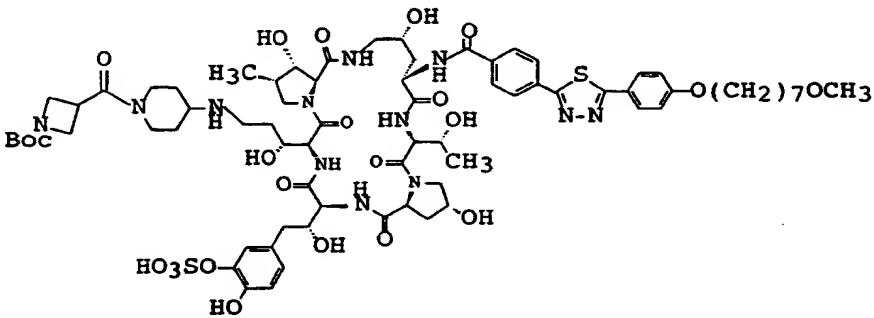
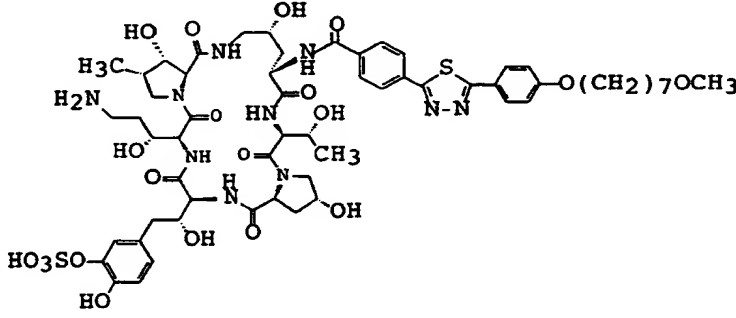
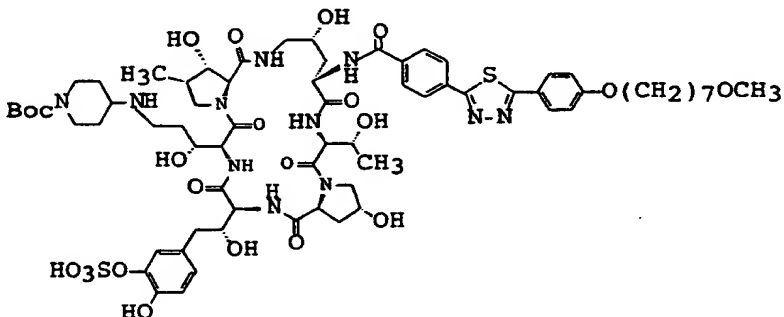
Example No.	Formula
121	
	
122	
	

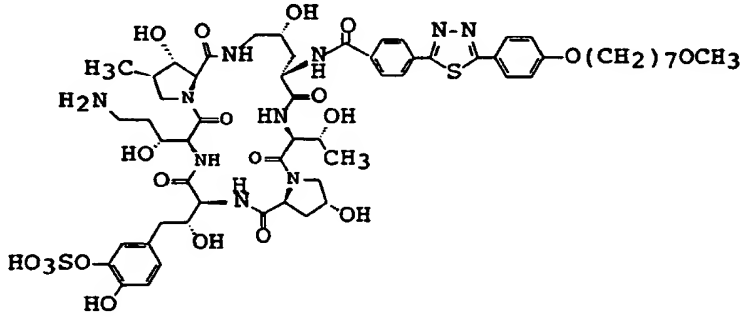
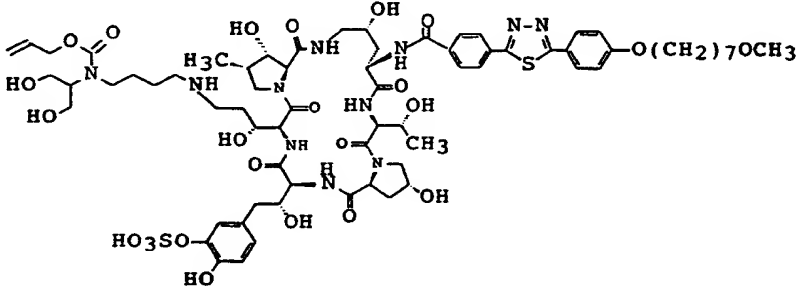
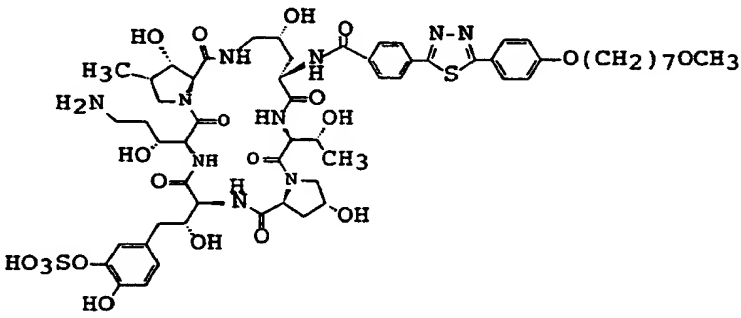
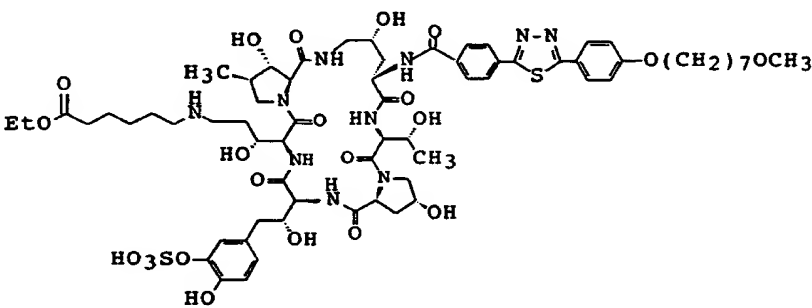
Example No.	Formula
123	
	
124	
	

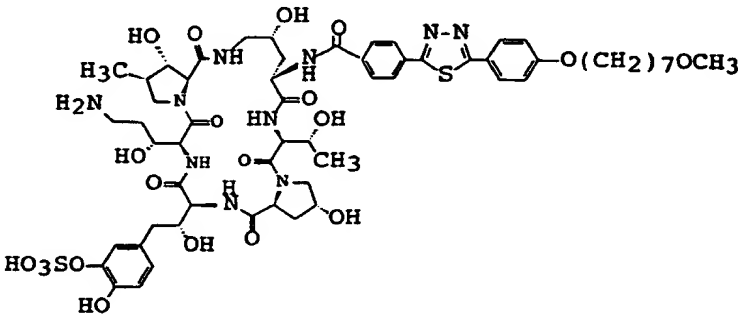
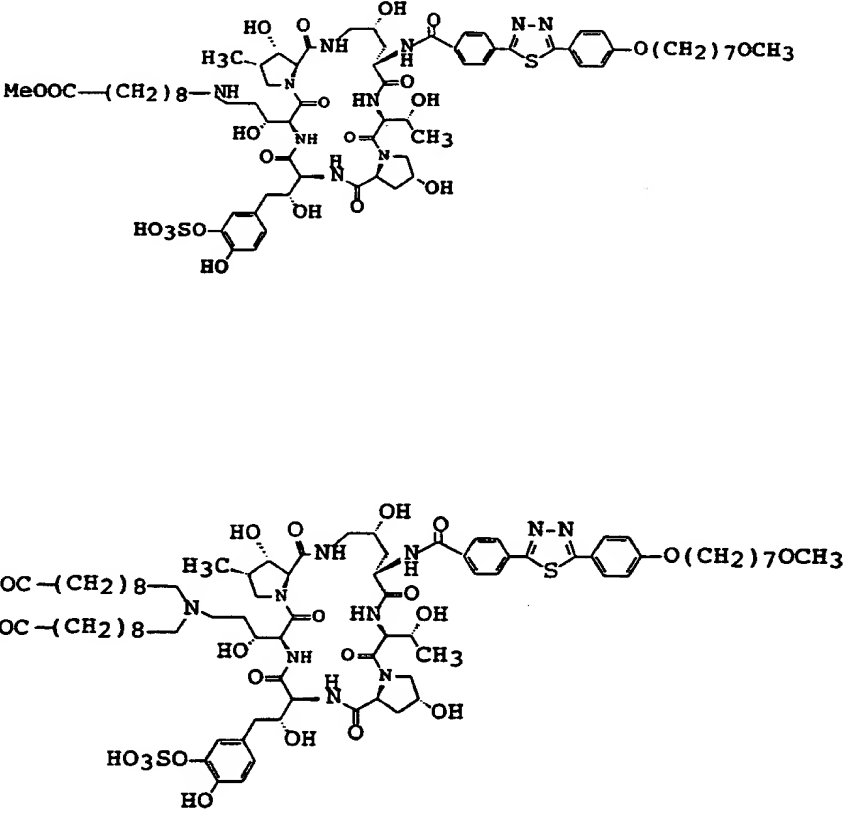
Example No.	Formula
125	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a sulfonate group (HO_3SO), and a long alkoxy chain ($\text{O}(\text{CH}_2)_7\text{OMe}$).</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different side chain (Me) and a different sulfonate group ($-\text{O}_3\text{SO}$).</p>
126	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different side chain (H_2N) and a different sulfonate group (HO_3SO).</p>
	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different side chain (Boc-NH) and a different sulfonate group (HO_3SO).</p>

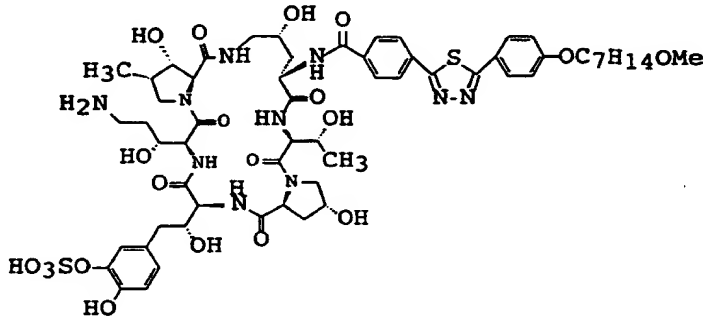
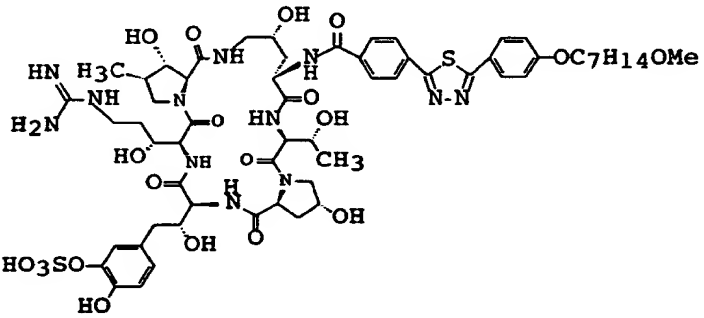
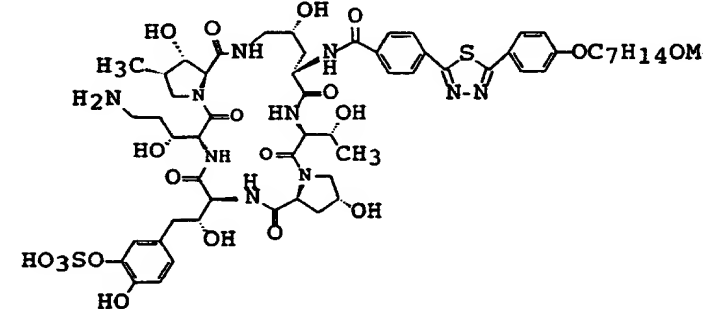
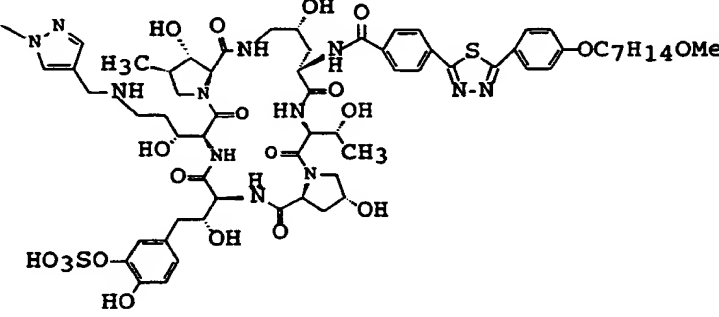
Example No.	Formula
127	
	
128	
	

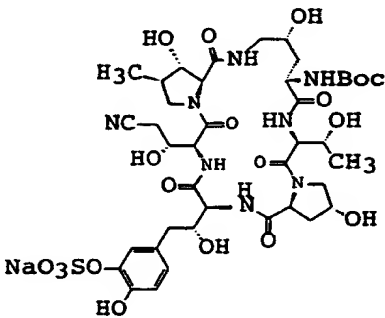
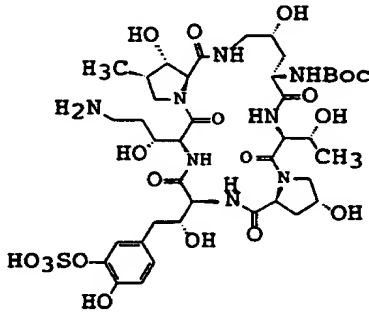
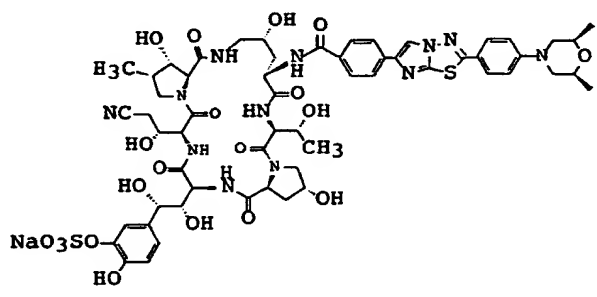
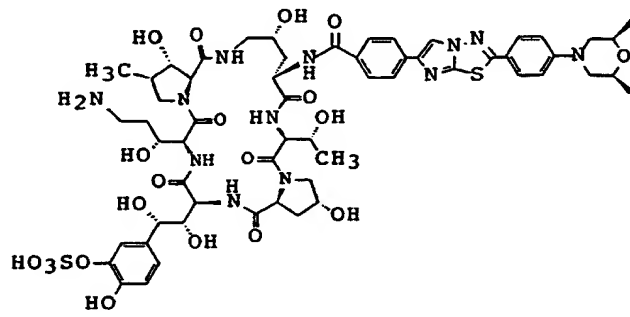
Example No.	Formula
129	
	
130	
	

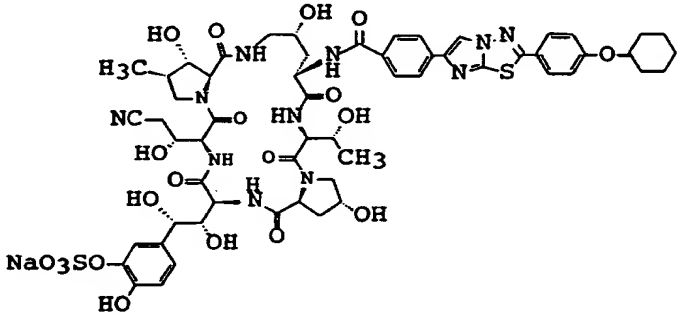
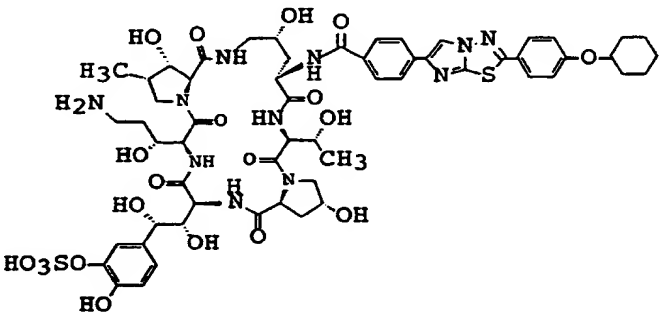
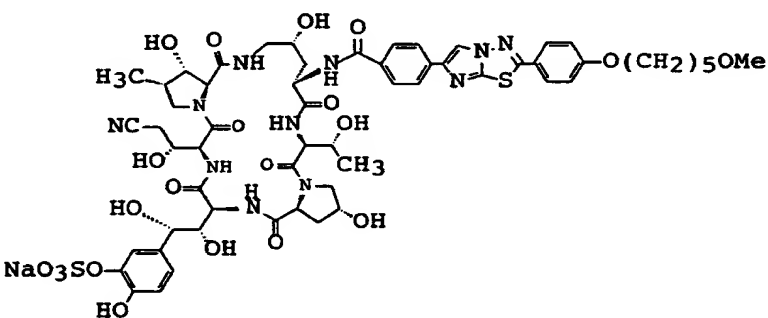
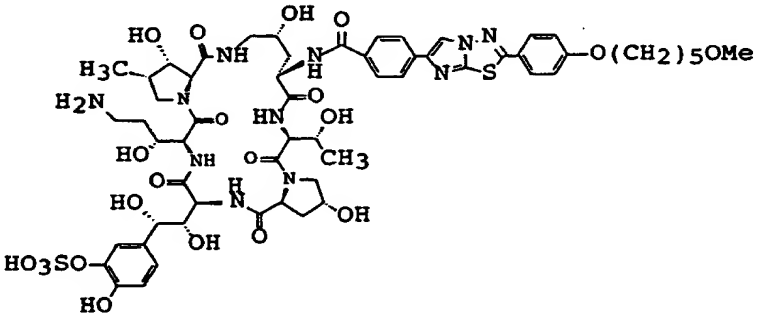
Example No.	Formula
131	
	
132	
	

Example No.	Formula
133	
	
134	
	

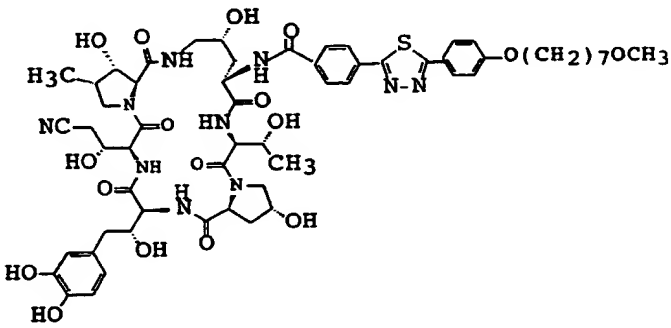
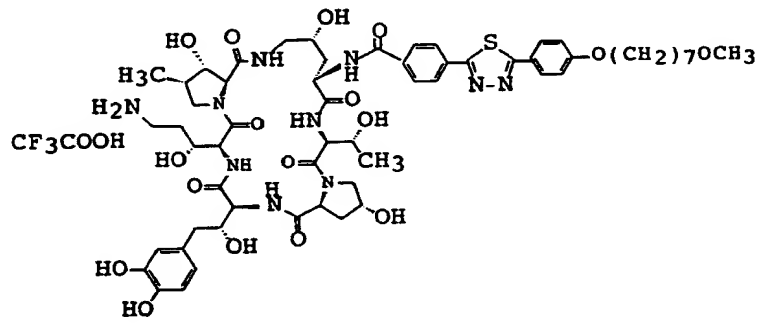
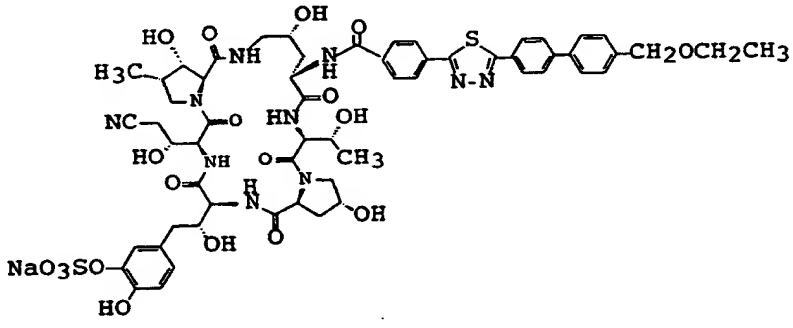
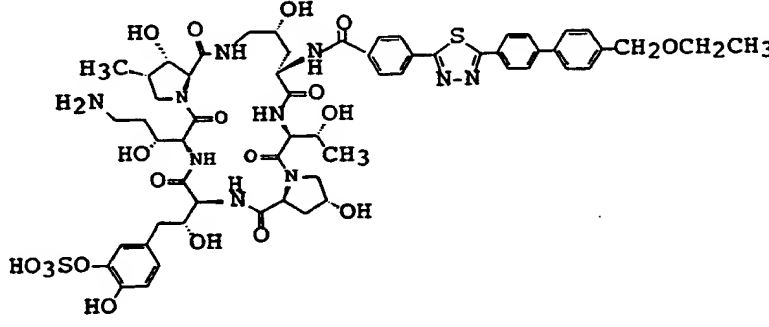
Example No.	Formula
135	
	

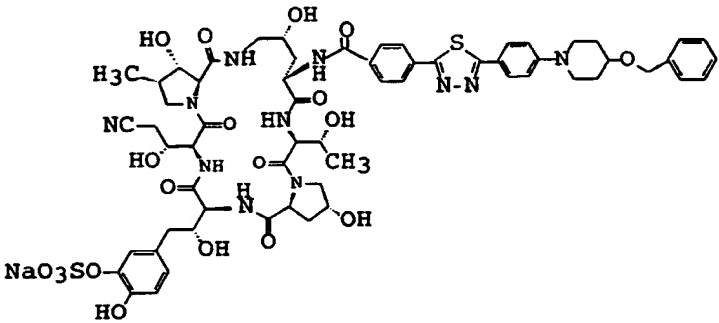
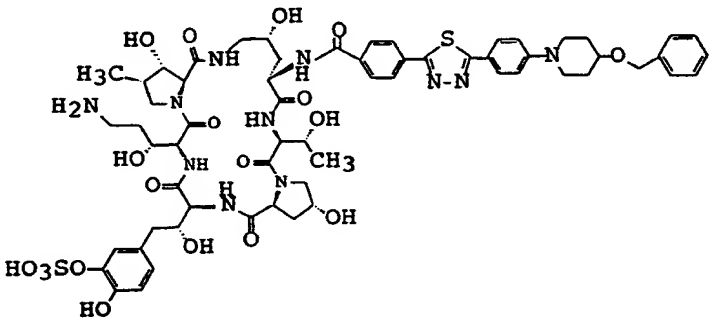
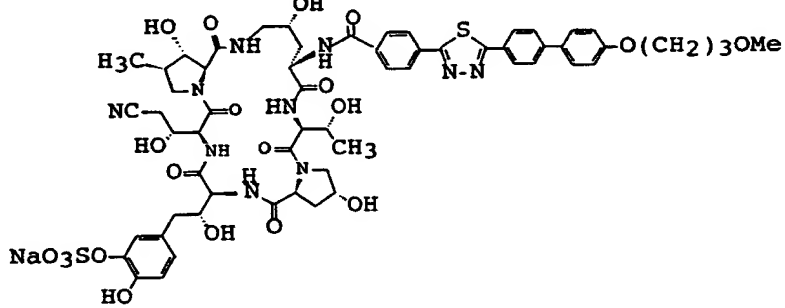
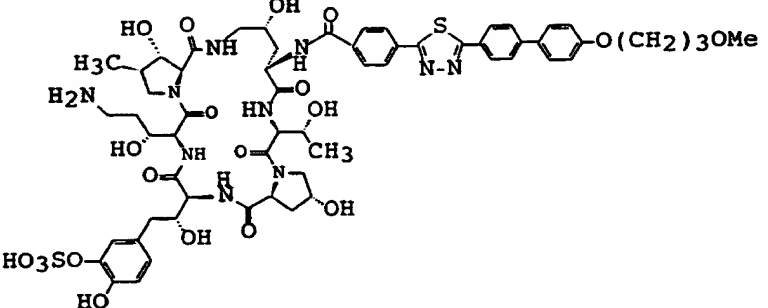
Example No.	Formula
136	
	
137	
	

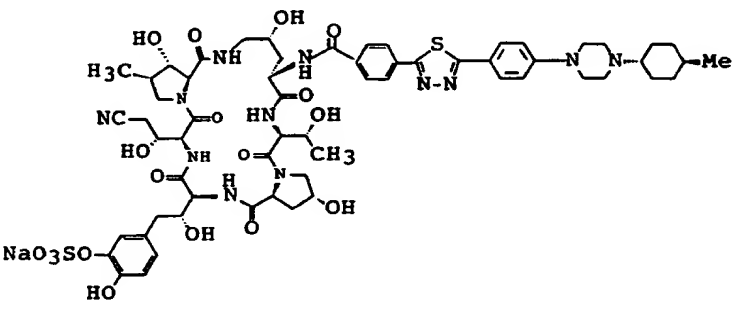
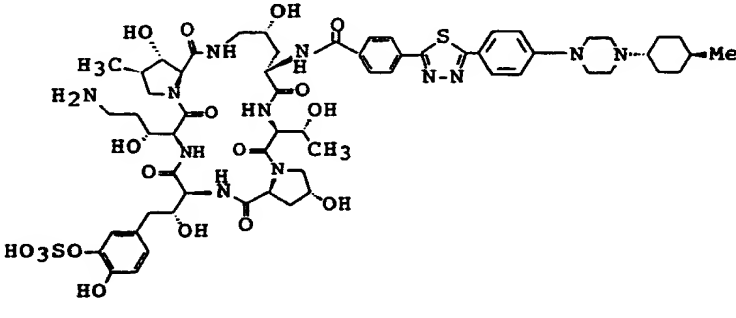
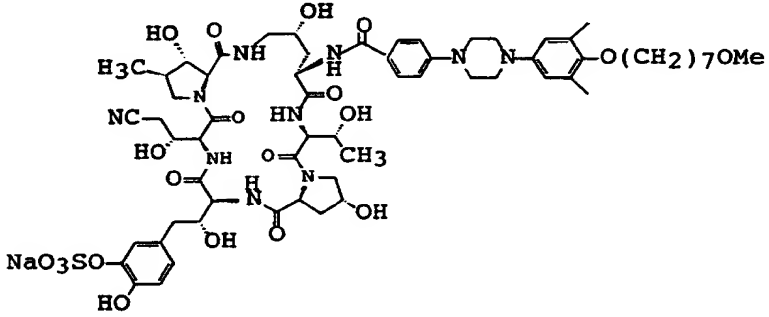
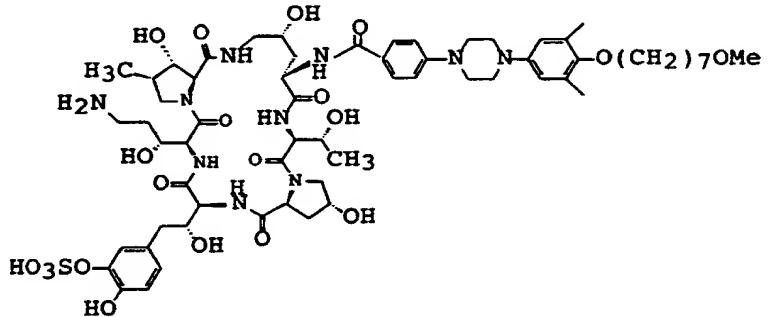
Example No.	Formula
138	
	
139	
	

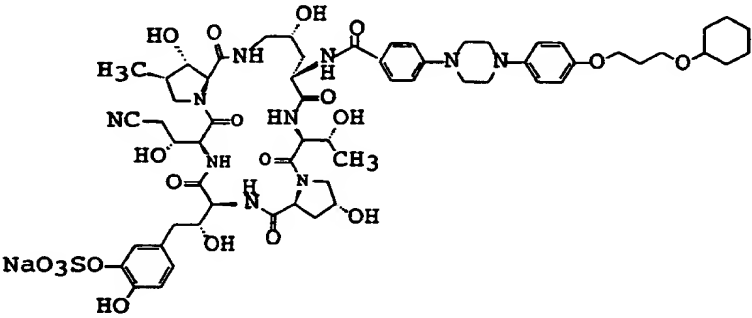
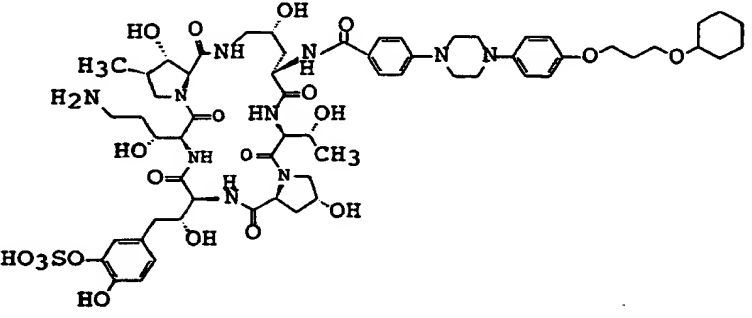
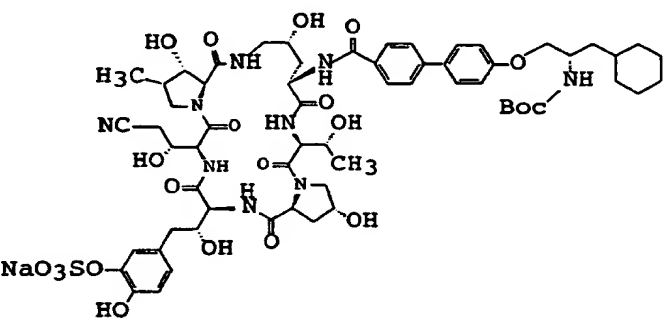
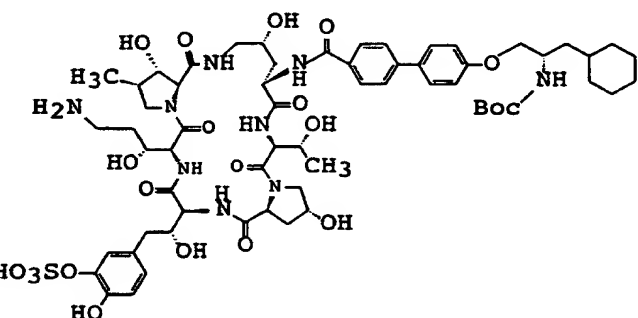
Example No.	Formula
140	
	
141	
	

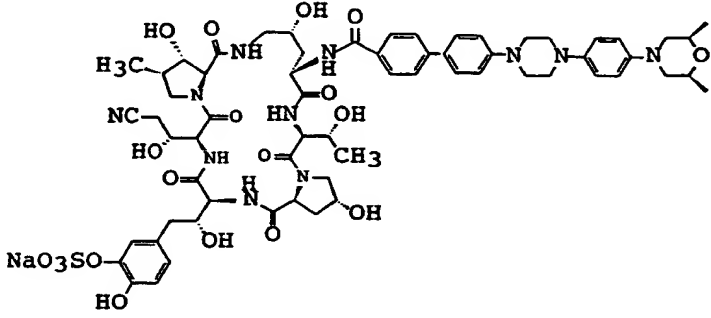
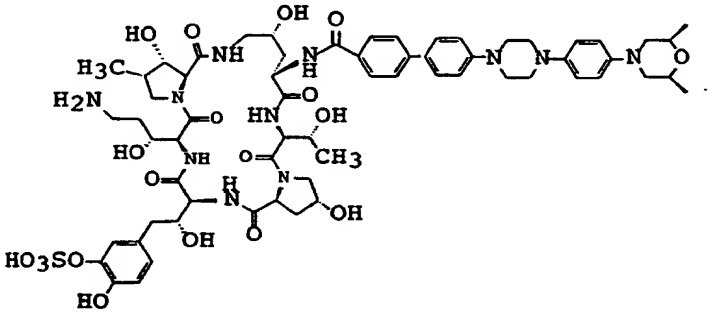
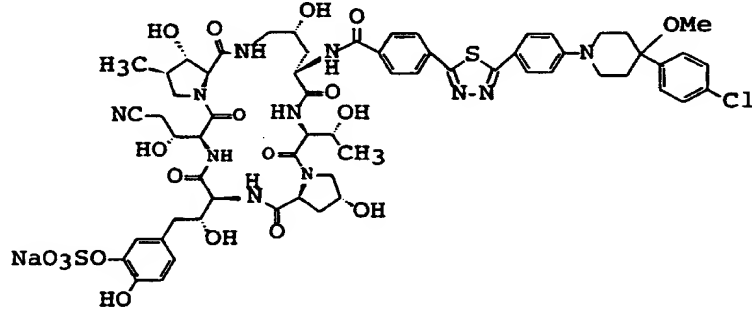
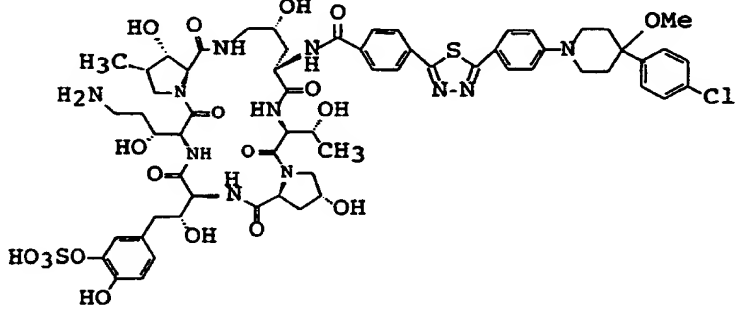
Example No.	Formula
142	
143	

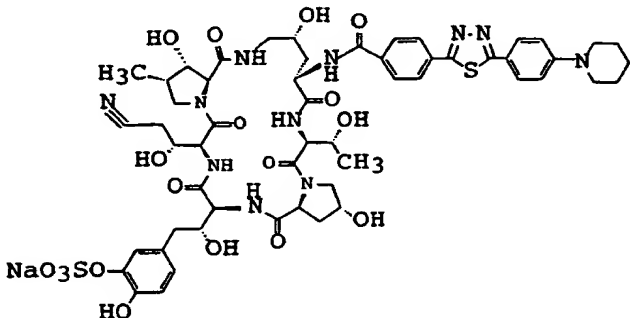
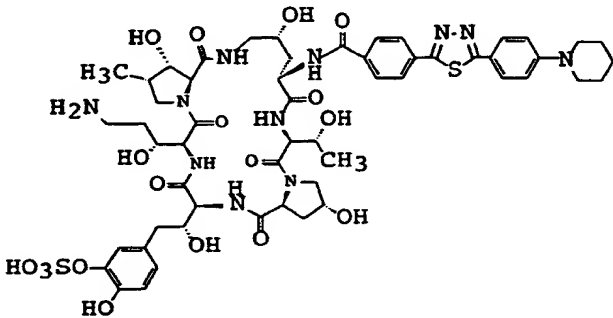
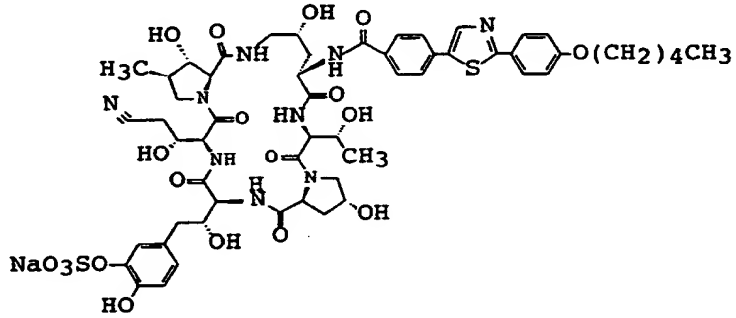
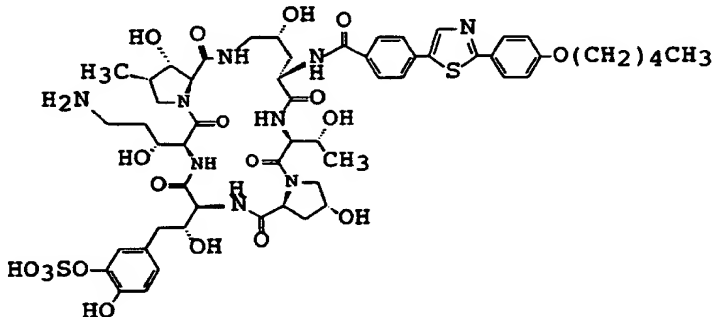
Example No.	Formula
144	
	
145	
	

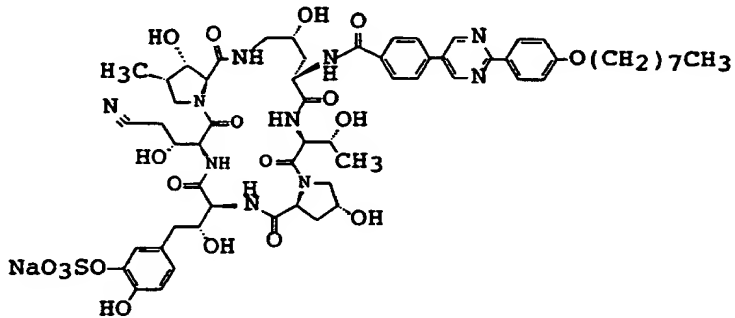
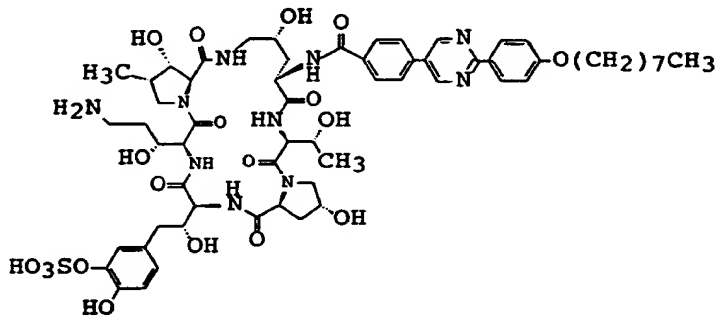
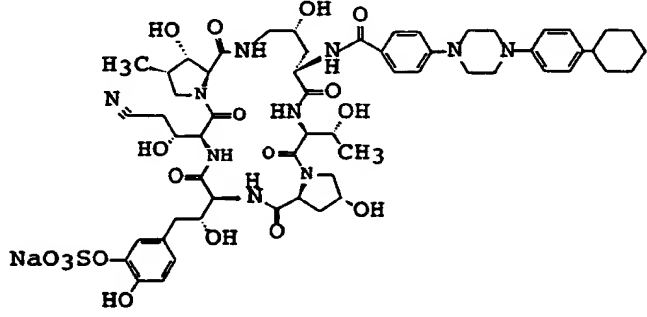
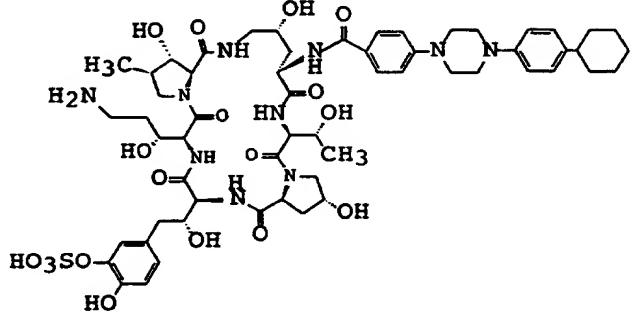
Example No.	Formula
146	
	
147	
	

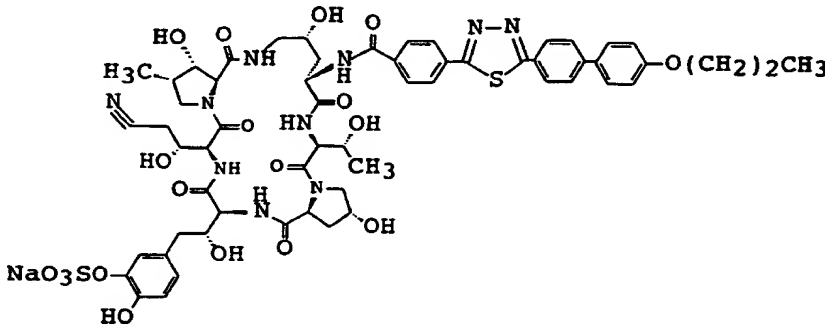
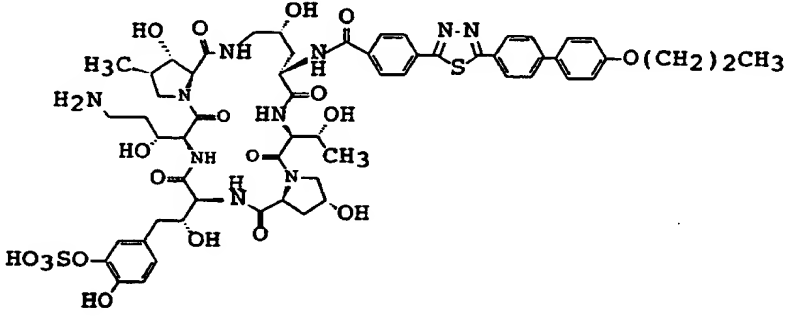
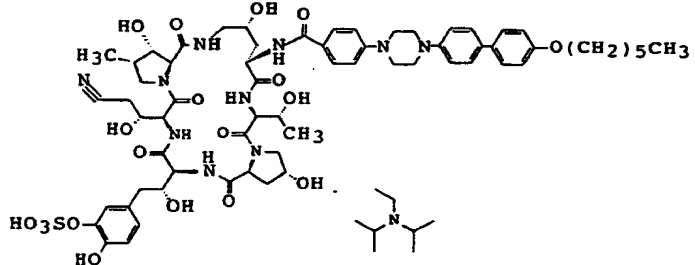
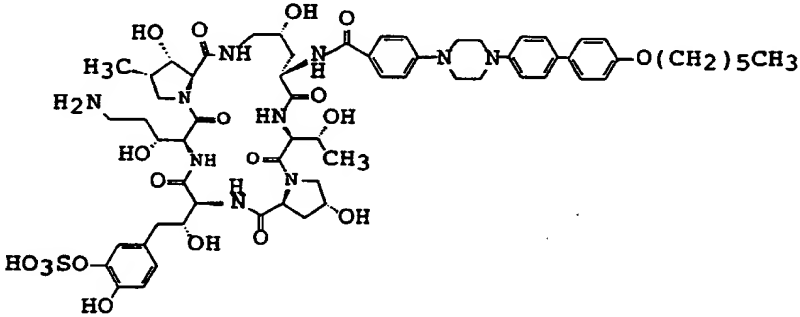
Example No.	Formula
148	
	
149	
	

Example No.	Formula
150	
	
151	
	

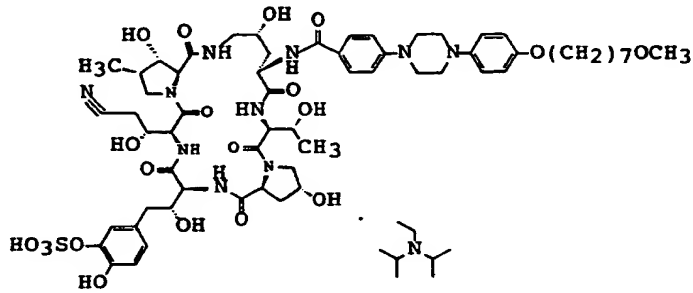
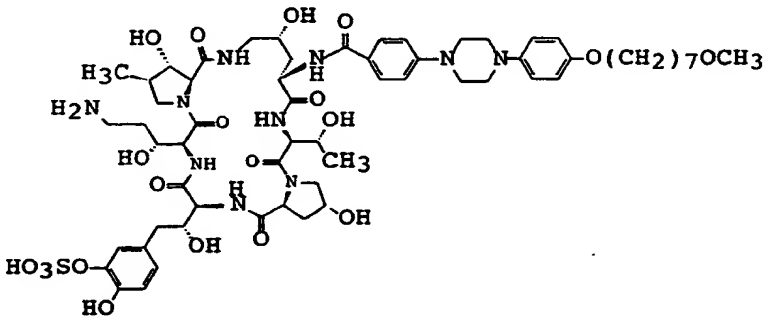
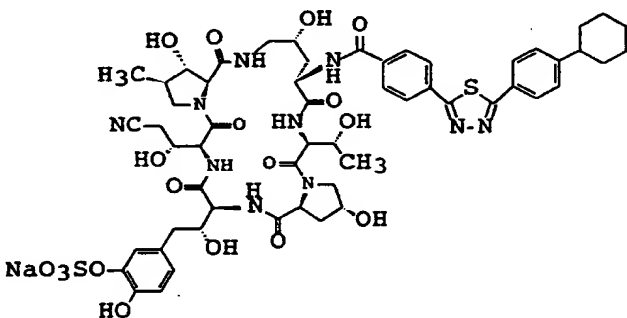
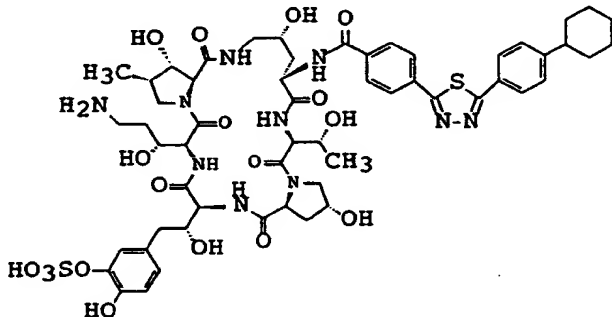
Example No.	Formula
152	
	
153	
	

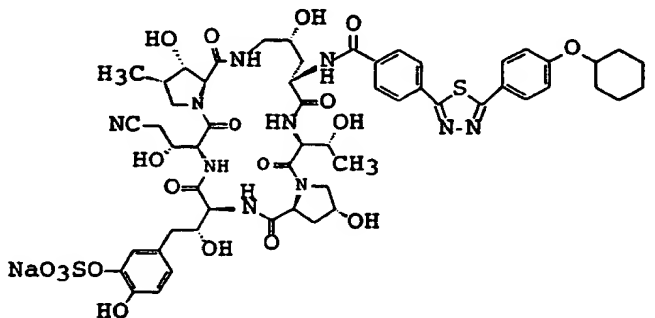
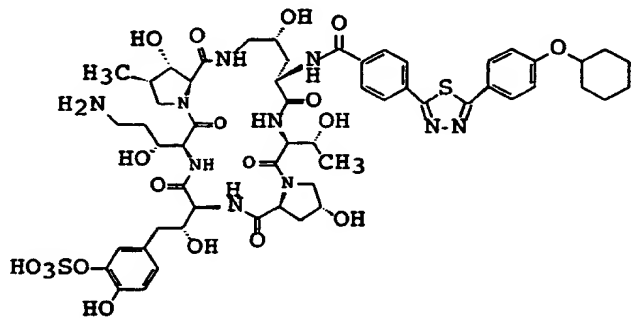
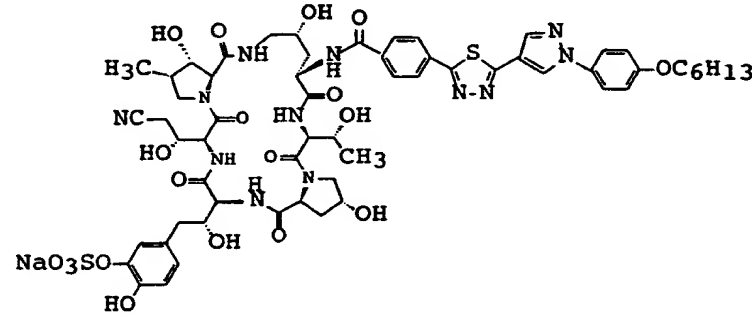
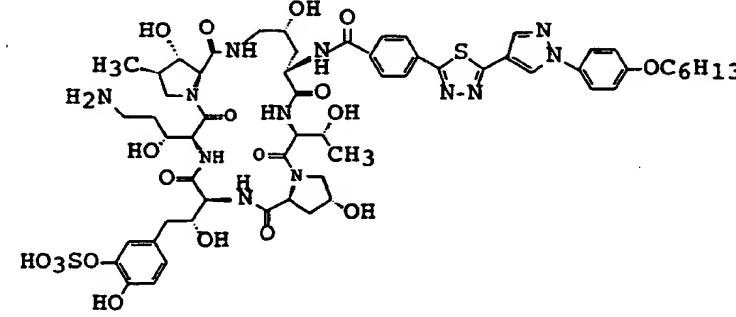
Example No.	Formula
154	
	
155	
	

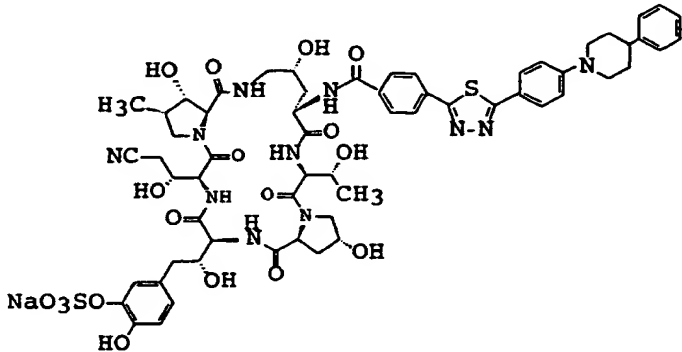
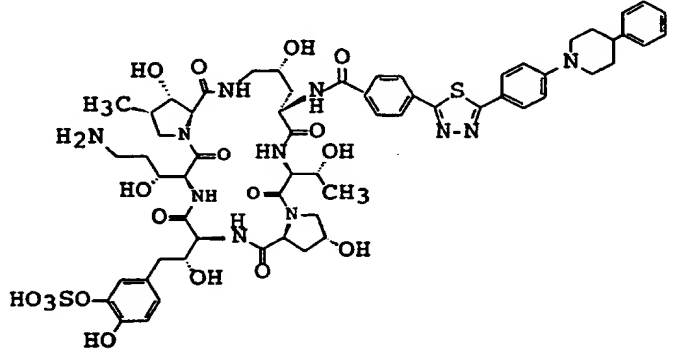
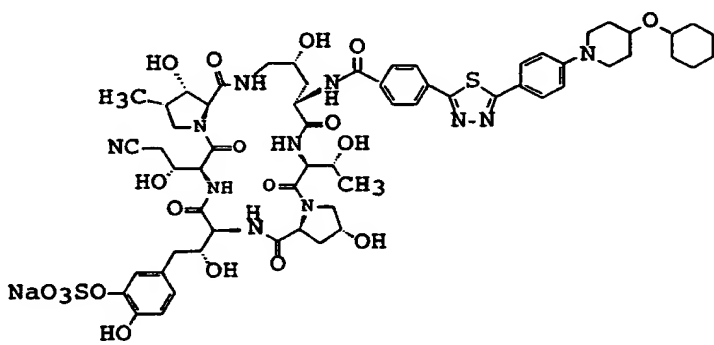
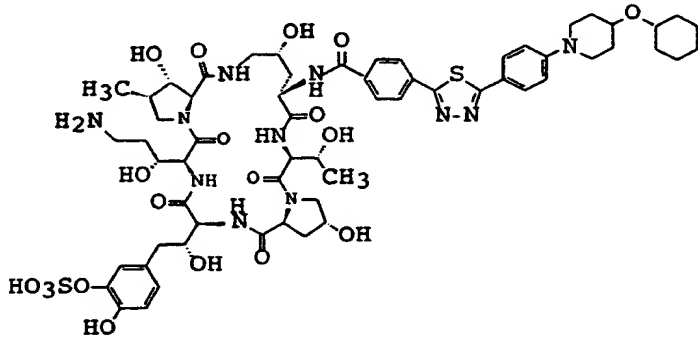
Example No.	Formula
156	
	
157	
	

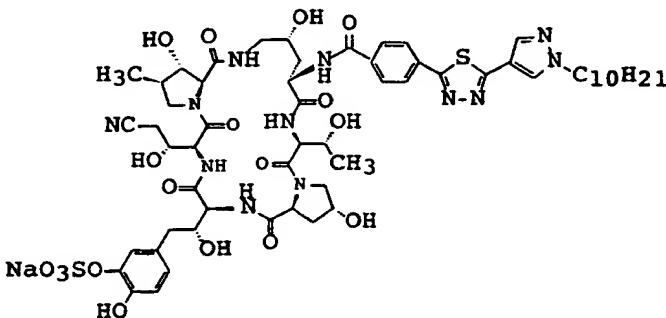
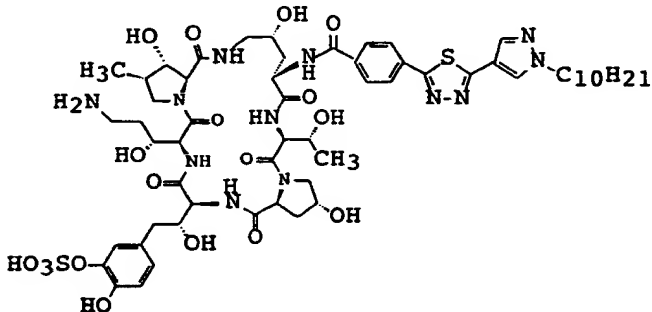
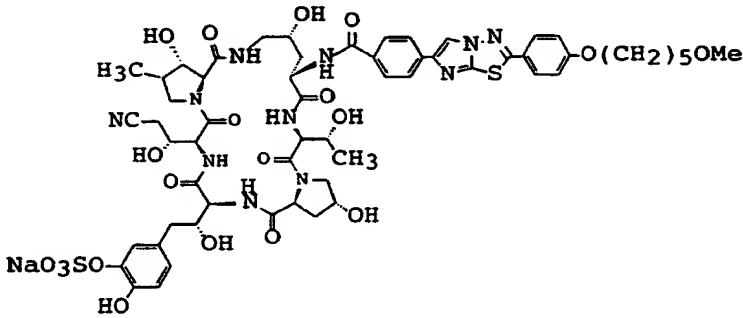
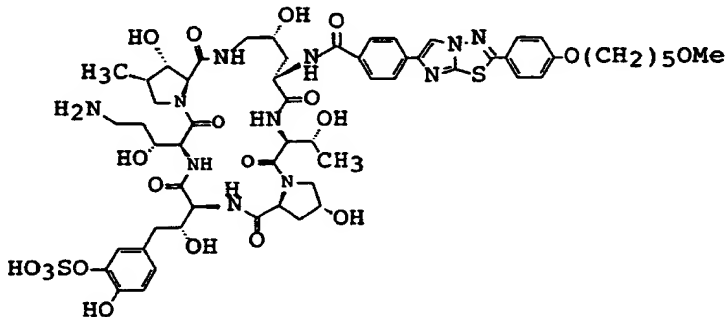
Example No.	Formula
158	
	
159	
	

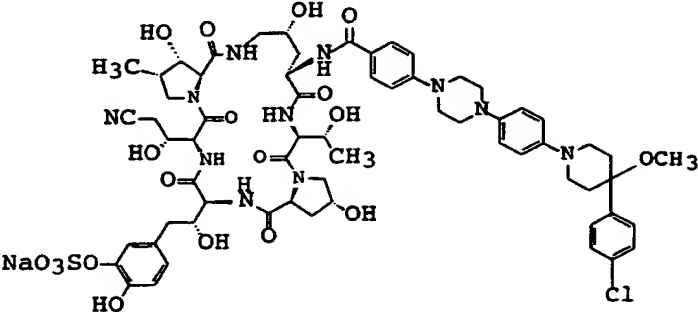
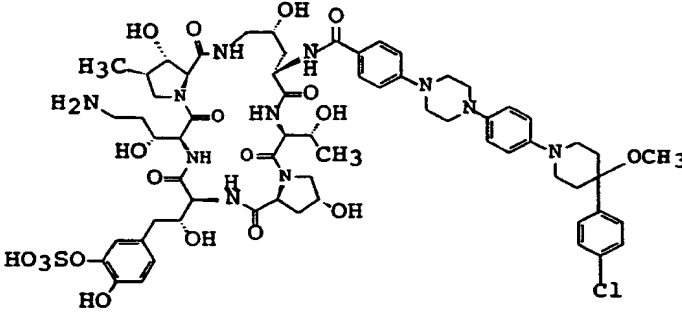
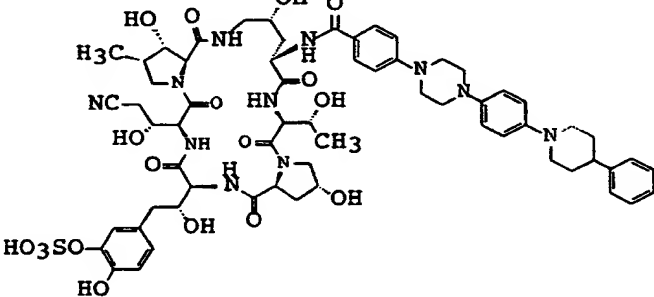
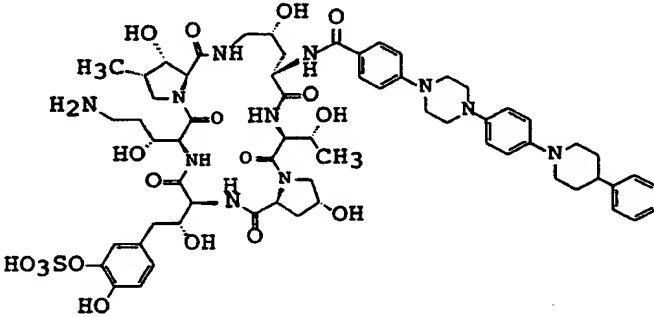
Example No.	Formula
160	
161	

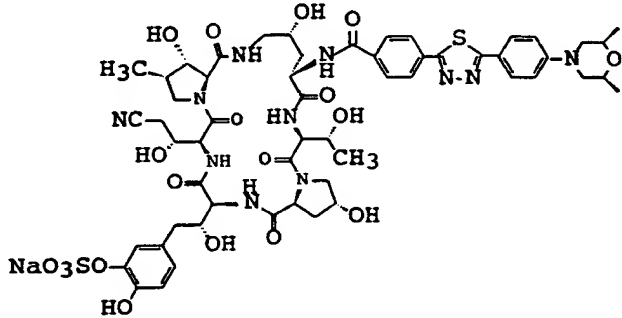
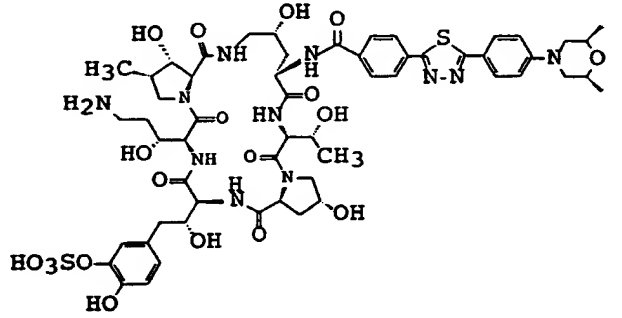
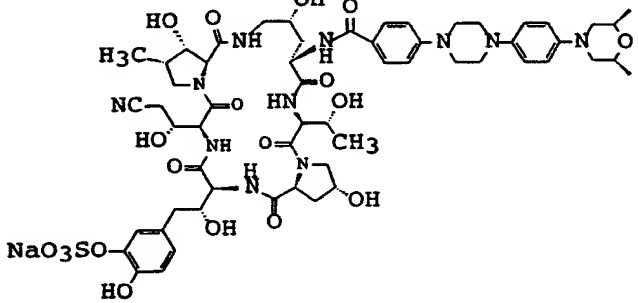
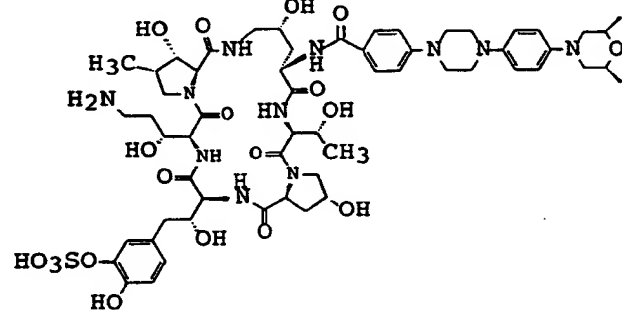
Example No.	Formula
162	
	
163	
	

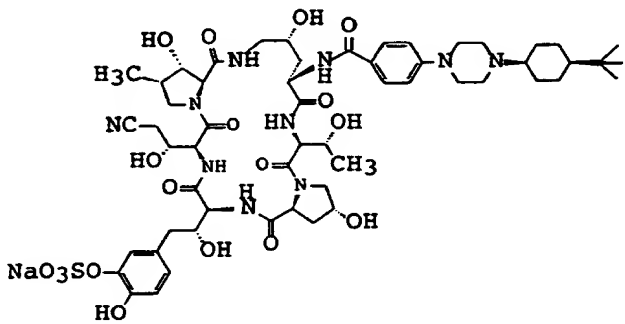
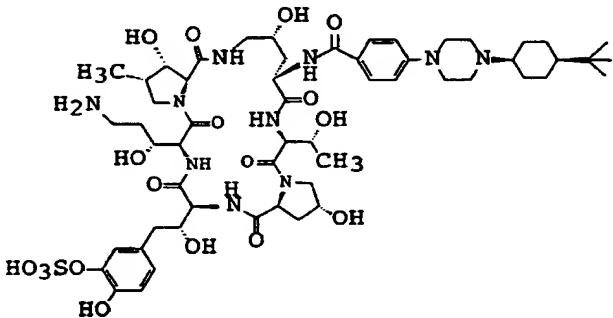
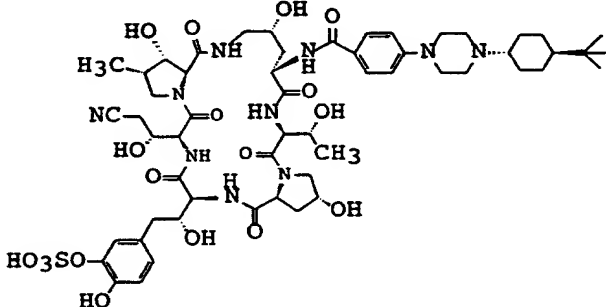
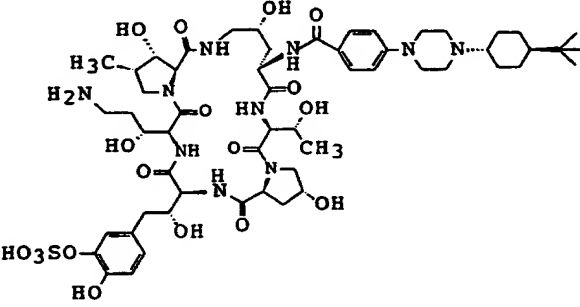
Example No.	Formula
164	
	
165	
	

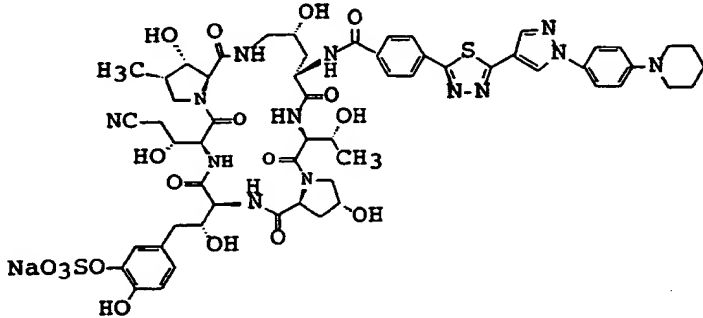
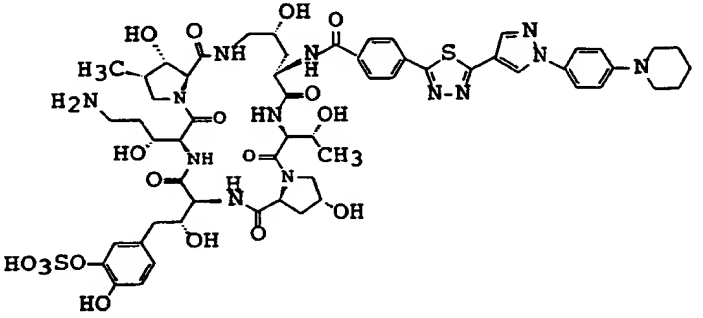
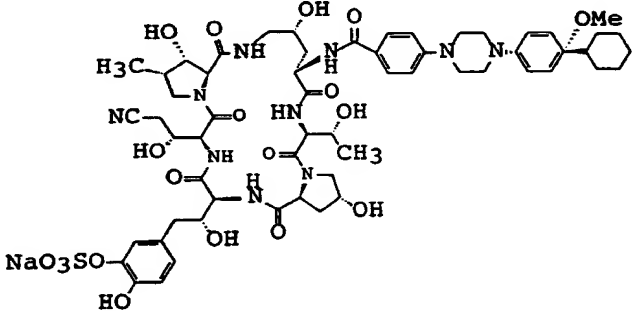
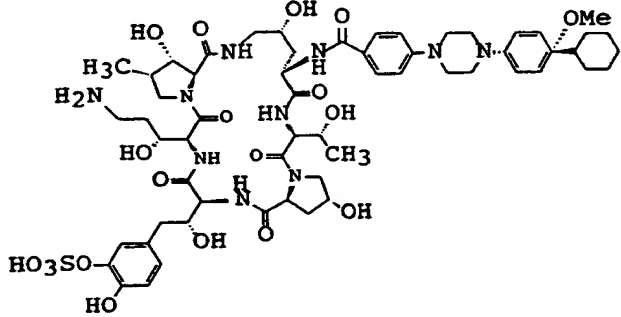
Example No.	Formula
166	
	
167	
	

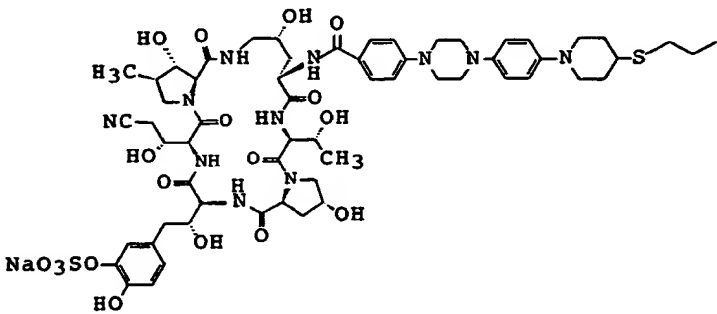
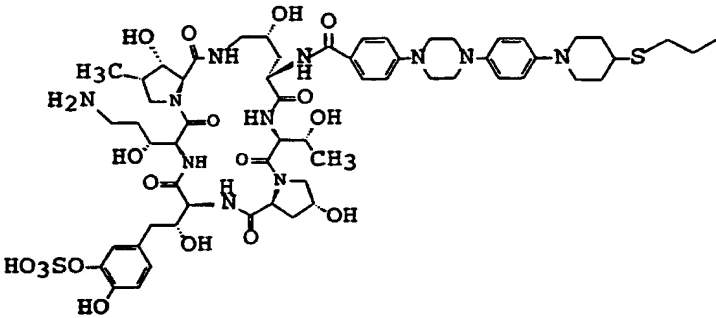
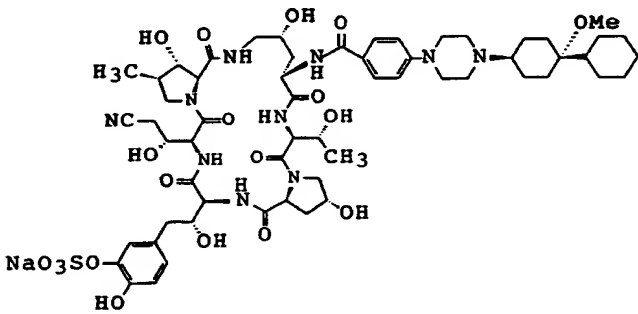
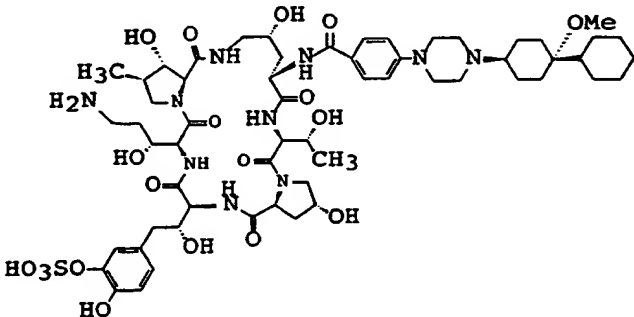
Example No.	Formula
168	
	
169	
	

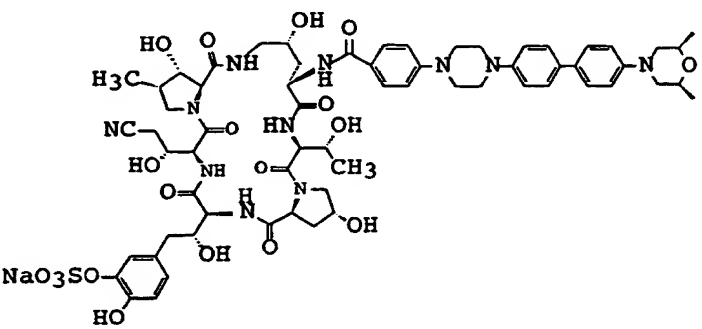
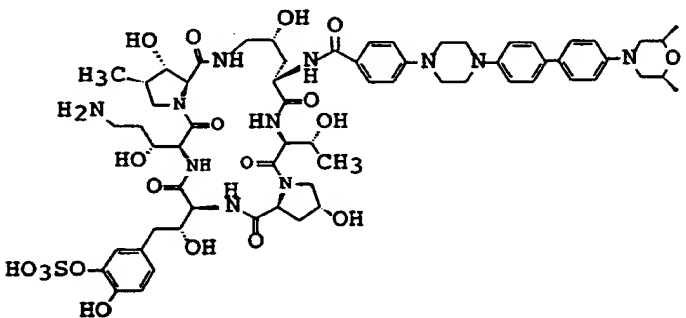
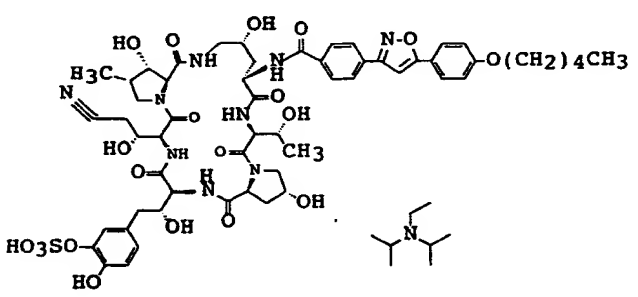
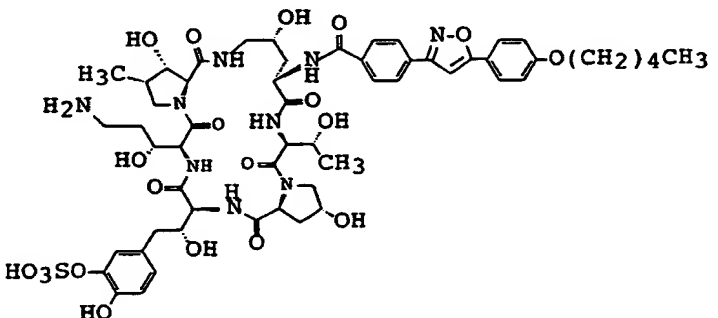
Example No.	Formula
170	
	
171	
	

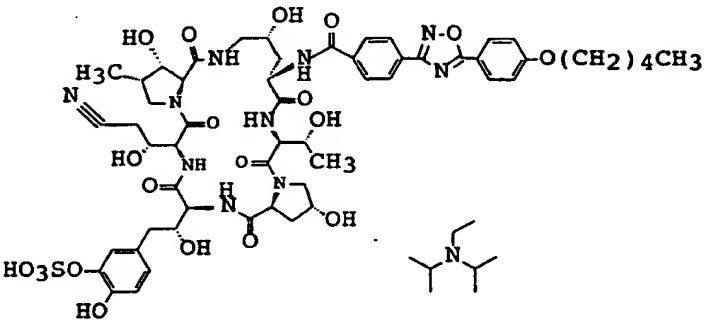
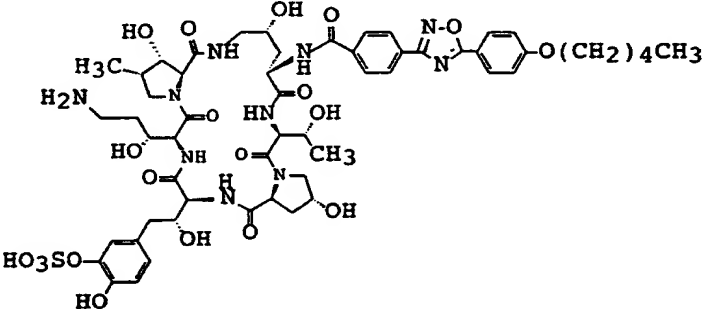
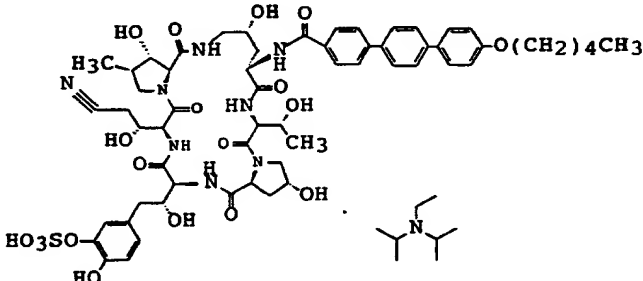
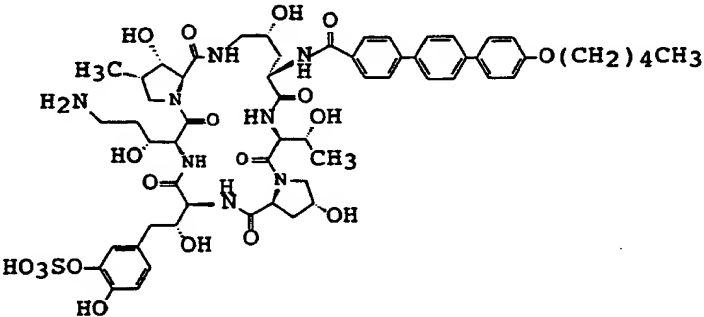
Example No.	Formula
172	
	
173	
	

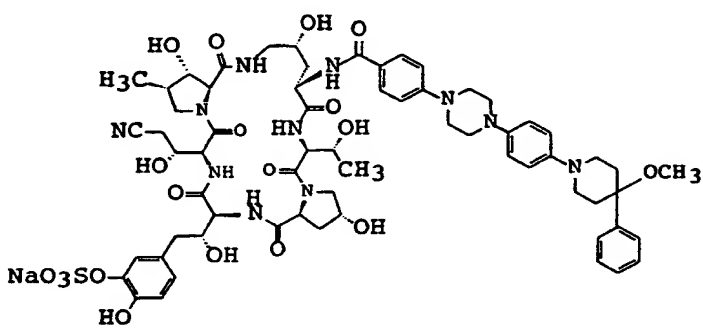
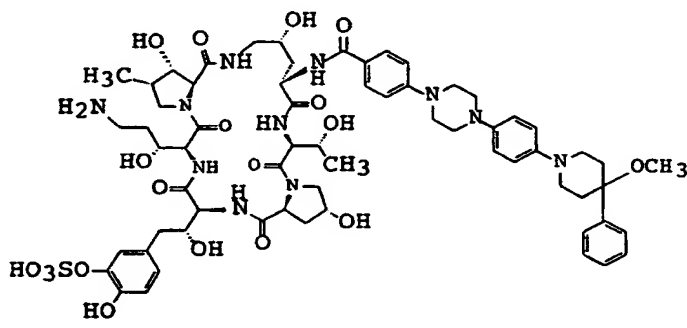
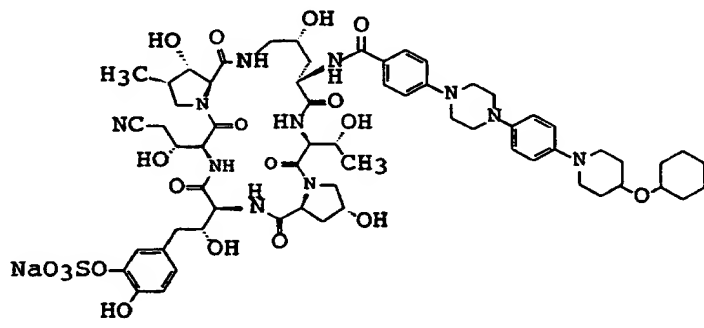
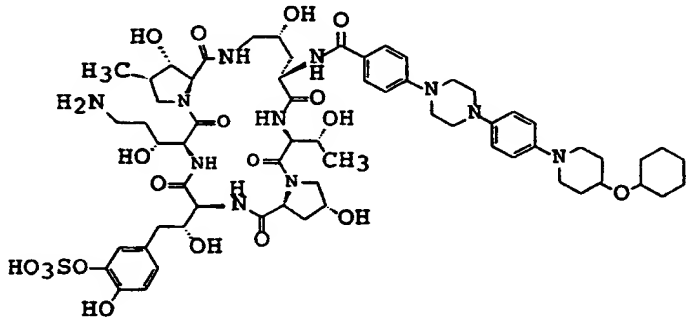
Example No.	Formula
174	
	
175	
	

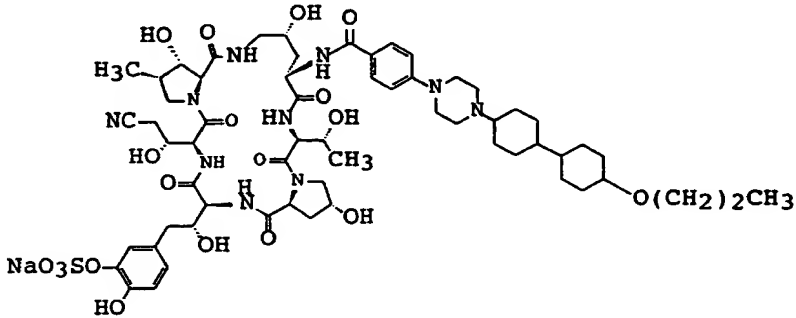
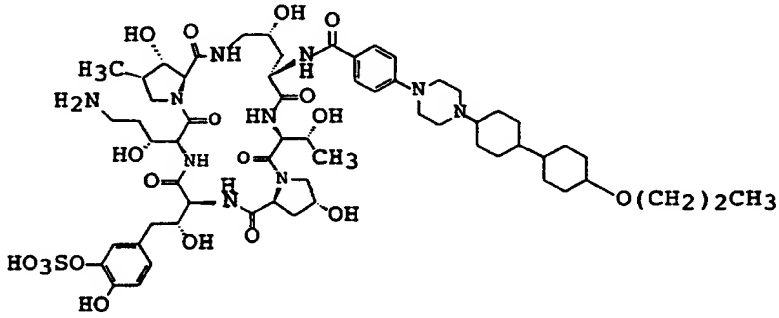
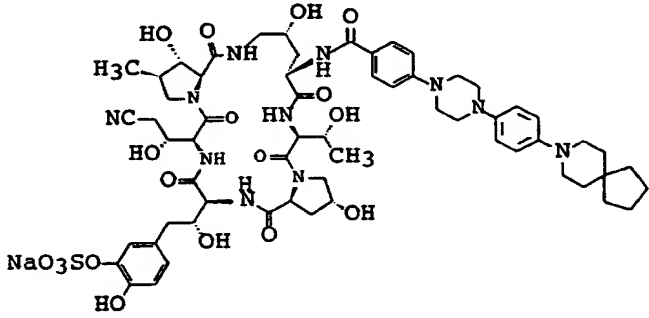
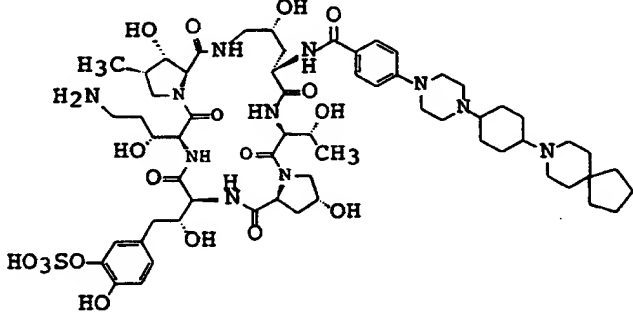
Example No.	Formula
176	
	
177	
	

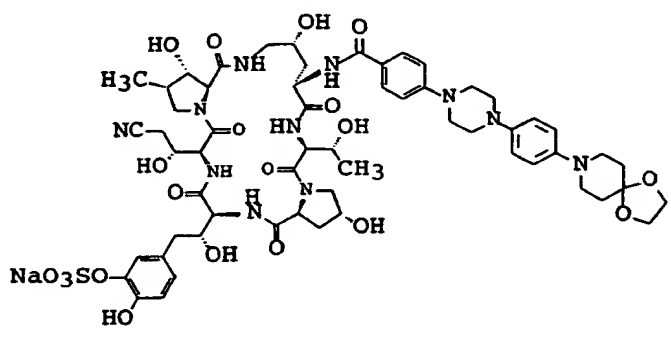
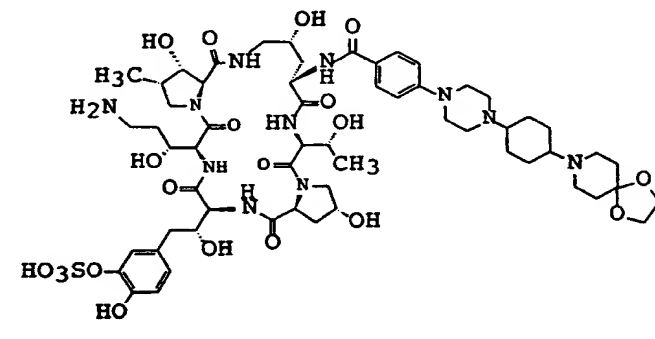
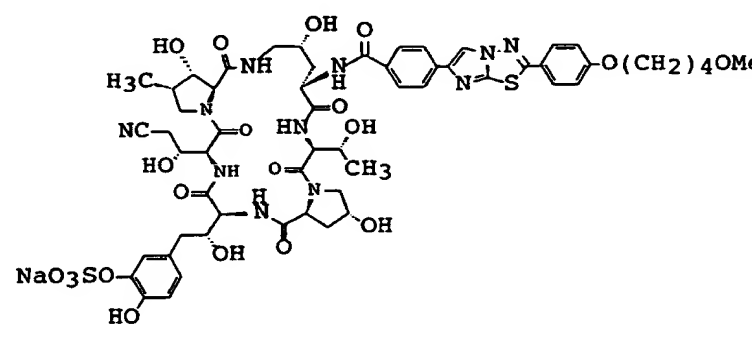
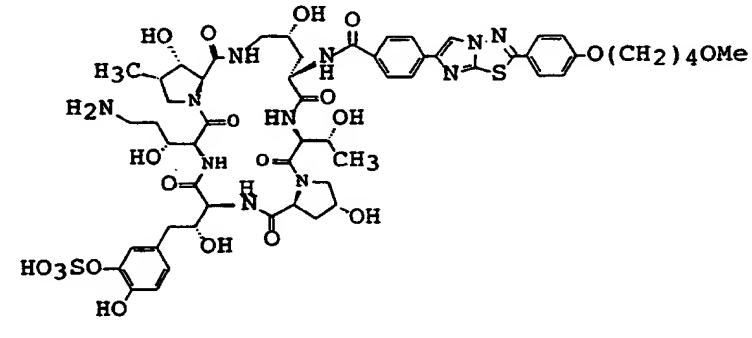
Example No.	Formula
178	
	
179	
	

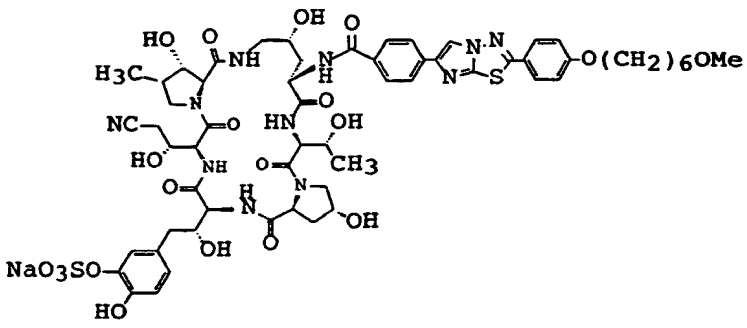
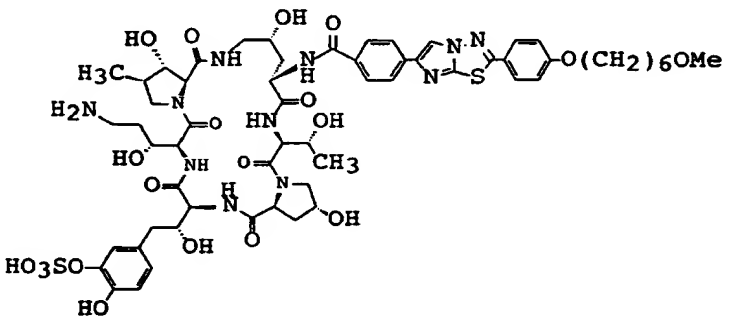
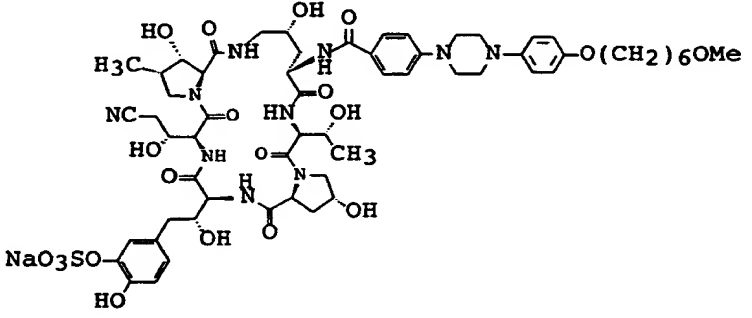
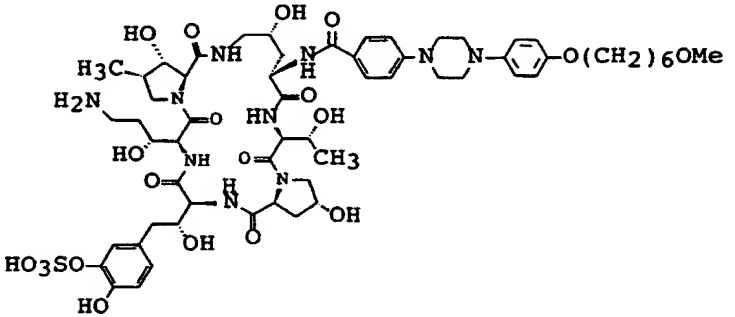
Example No.	Formula
180	
	
181	
	

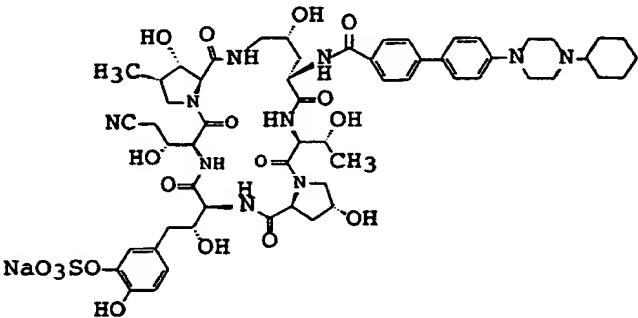
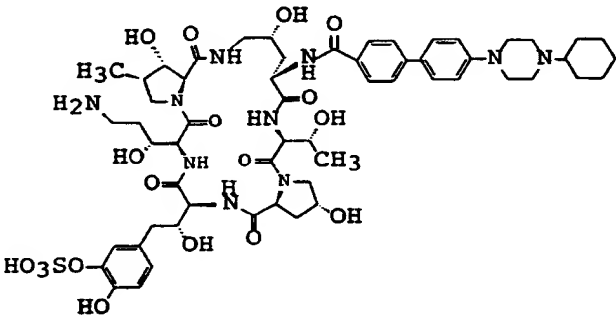
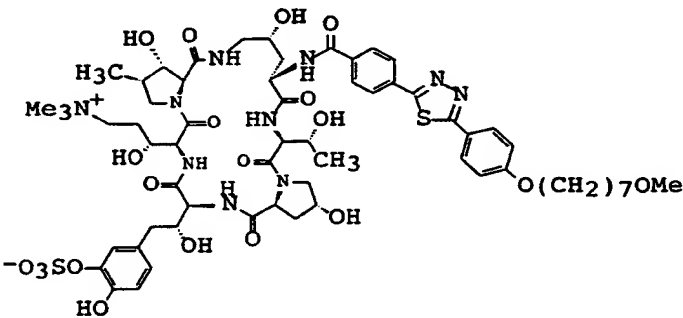
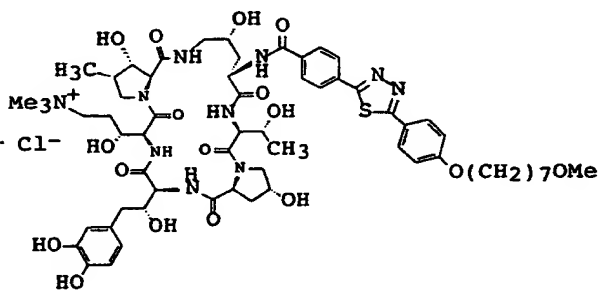
Example No.	Formula
182	
	
183	
	

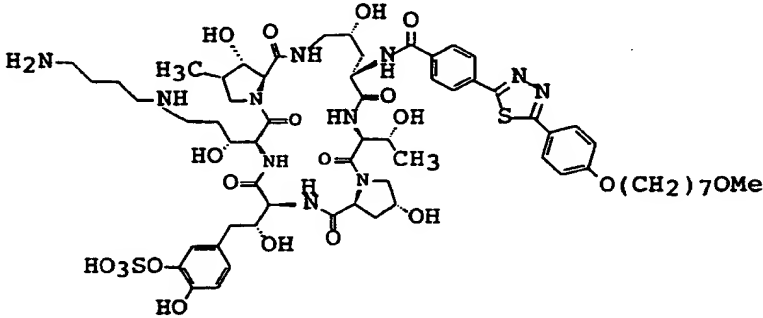
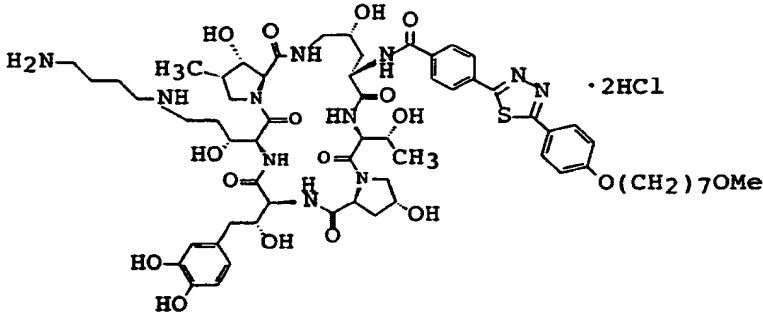
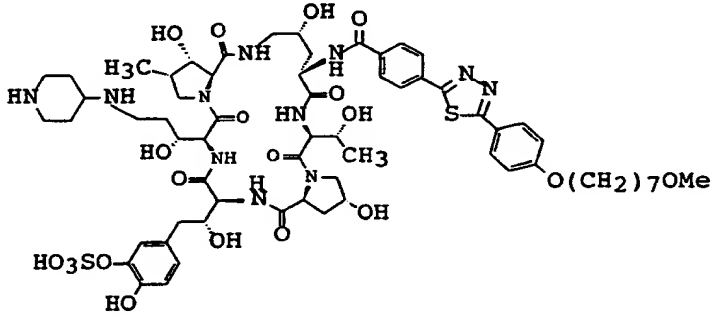
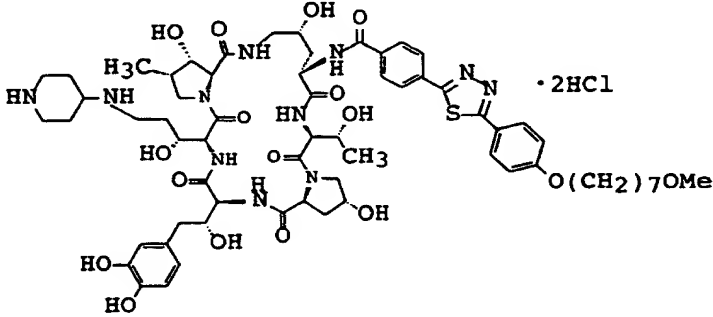
Example No.	Formula
184	
	
185	
	

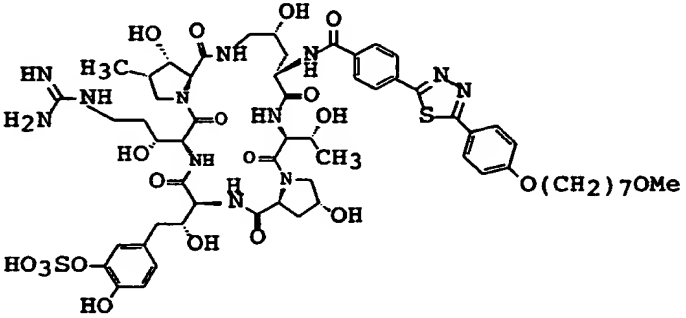
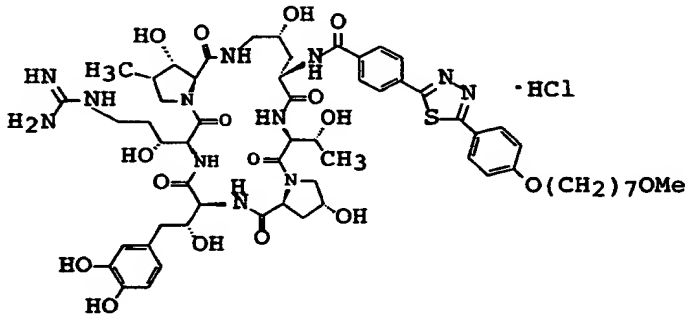
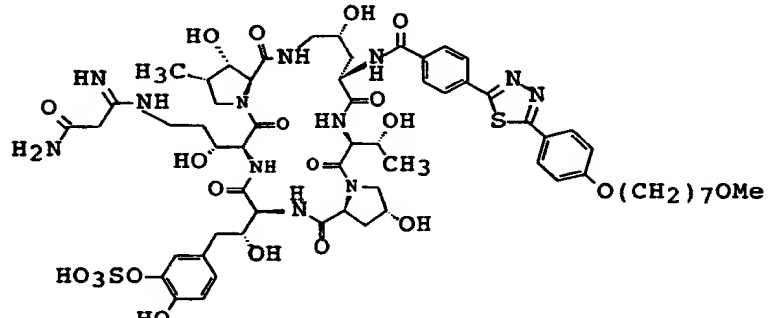
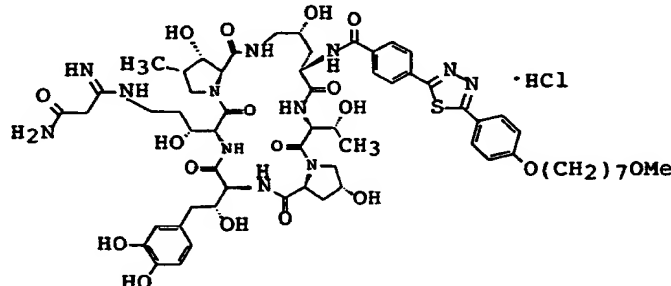
Example No.	Formula
186	
	
187	
	

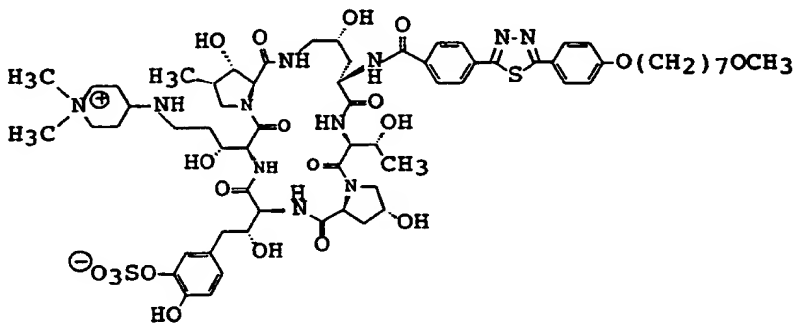
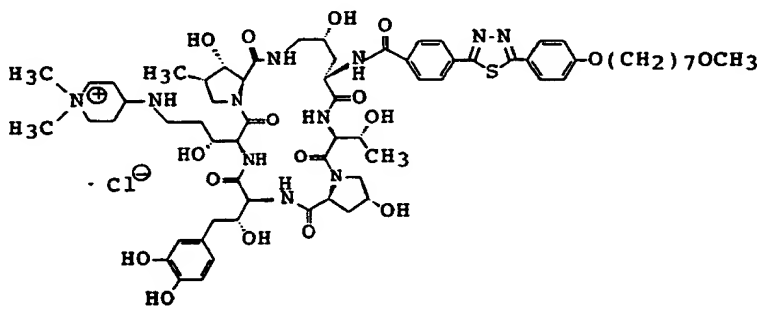
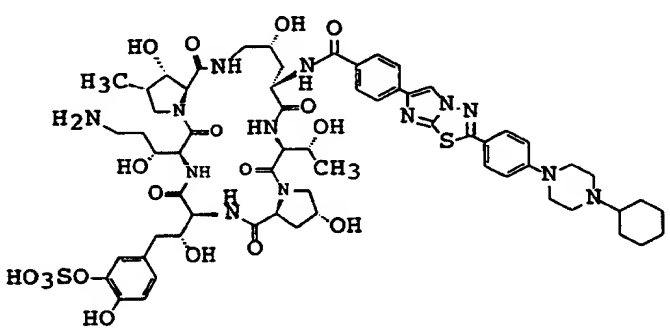
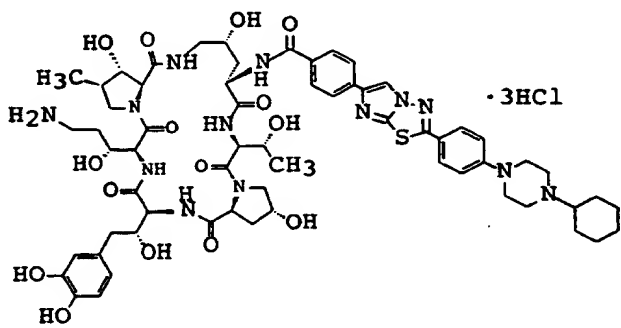
Example No.	Formula
188	
	
189	
	

Example No.	Formula
190	
	
191	
	

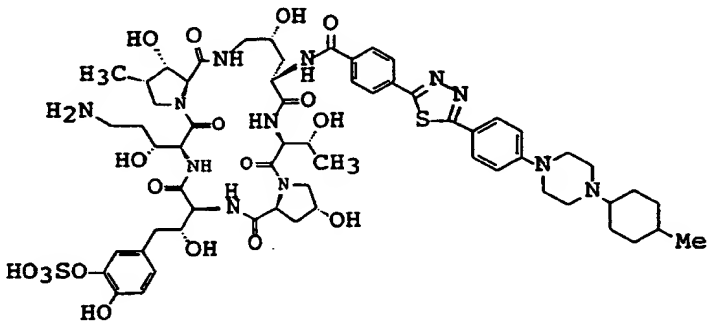
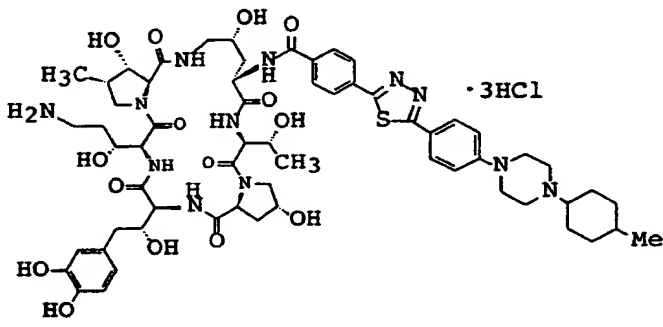
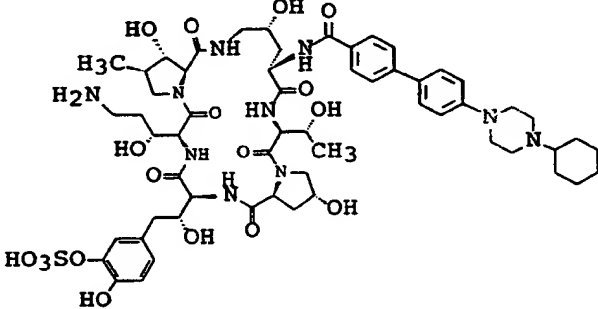
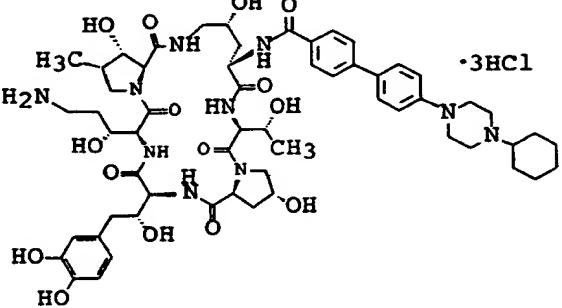
Example No.	Formula
192	
	
193	
	

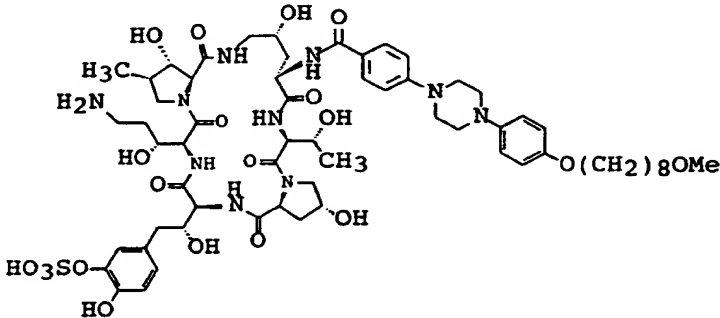
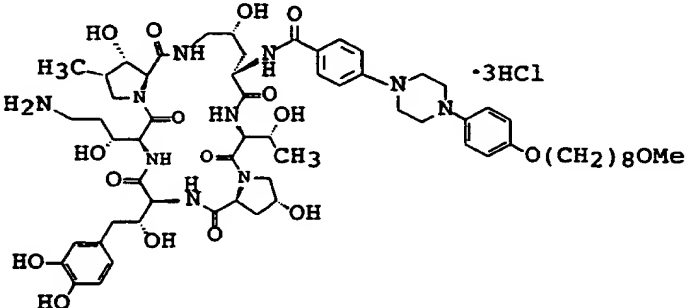
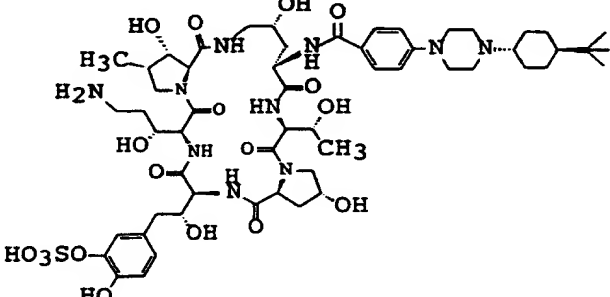
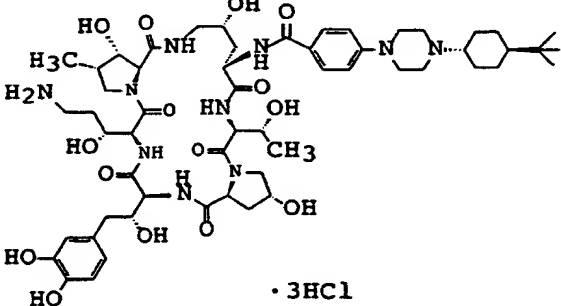
Example No.	Formula
194	
	
195	
	

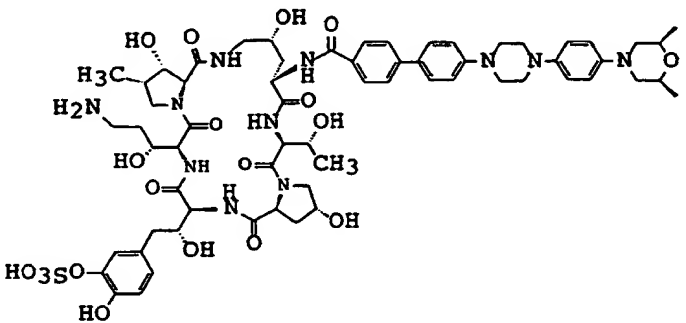
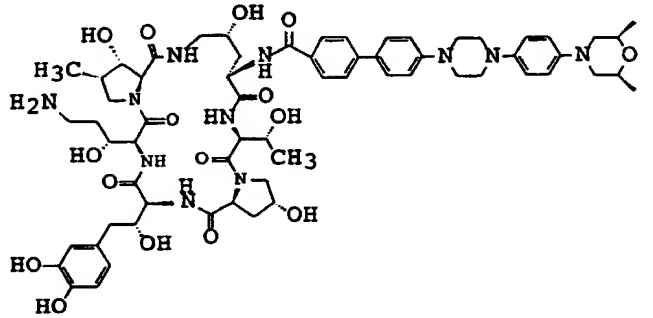
Example No.	Formula
196	
	
197	
	

Example No.	Formula
198	
	
199	
	

Example No.	Formula
200	
201	

Example No.	Formula
202	
	
203	
	

Example No.	Formula
204	
	
205	
	

Example No.	Formula
206	
	

Example 22

A solution of starting compound (22) (670 mg) and 10%
 5 palladium on carbon (50%, including water) (0.8 g) in a
 mixture of methanol (10 ml) and water (10 ml) was
 hydrogenated under an atmospheric pressure of hydrogen with
 stirring at ambient temperature for 12 hours. The catalyst
 was filtered off and washed with a mixture of methanol and
 10 water (1:1 v/v) (50 ml), and the filtrate and washes were
 combined. To the solution was added dropwise
 allyloxycarbonyl chloride (3.0 ml) adjusting pH to 8.5-10.0
 with 1N sodium hydroxide with stirring on an ice-bath. The
 mixture was stirred at the same temperature for 2 hours and
 15 concentrated in vacuo. The resulting residue was dissolved
 in 1N sodium hydroxide (20 ml) and allowed to stand at 4°C
 overnight. The solution was subjected to column

chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 10% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (22) (379 mg).

NMR (DMSO- d_6 + D₂O, δ): 0.96 (3H, d, J=6.73Hz), 1.07 (3H, broad s), 1.36 (9H, s), 1.40-2.40 (8H, m), 2.70-3.45 (5H, m), 2.01 (3H, d, J=4.26Hz), 3.21 (3H, s), 3.31 (4H, t, J=6.34Hz), 3.70-4.50 (14H, m), 4.85-4.90 (2H, m), 3.60-4.95 (18H, m), 6.69 (1H, d, J=8.25Hz), 6.75 (1H, d, J=9.54Hz), 6.98 (1H, s)

ESI MASS (m/z)(Negative): 1135.3 (M^+ +Na)

Example 23

To a solution of starting compound (23) (1.0 g) in DMF (10 ml) were added 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.30 g) and diisopropylethylamine (0.27 ml) with stirring at ambient temperature, and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture was added pH 6.86 standard buffer solution (100 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 20% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (23) (302 mg).

IR (KBr): 1668, 1633, 1516, 1441, 1277, 1252 cm^{-1}

NMR (DMSO- d_6 + D₂O, δ): 0.97 (3H, d, J=6.64Hz), 1.07 (3H, d, J=5.96Hz), 1.37 (9H, s), 1.40-2.00 (4H, m), 2.10-2.50 (4H, m), 2.60-3.40 (6H, m), 3.60-4.50 (10H, m), 4.65-4.85 (2H, m), 6.71 (1H, d, J=8.14Hz), 6.78 (1H, d, J=8.39Hz), 6.98 (1H, s)

ESI MASS (m/z)(Negative): 989.3 (M^+-1)

Elemental Analysis Calcd. for $C_{40}H_{62}N_8O_{19}S \cdot 5H_2O$:

C 44.44, H 6.71, N 10.36

Found: C 44.23, H 6.42, N 9.82

5

Example 24

A solution of starting compound (24) (211 mg), 1-methylpyrazole-4-carboxaldehyde (21.4 mg), acetic acid (29.2 mg) and sodium cyanoborohydride (13.3 mg) in 1:1 methanol-N,N-dimethylformamide (6 ml) was stirred 2 days at room temperature, then treated with ethyl acetate and the precipitate was collected, washed with ethyl acetate and dried. This crude material was dissolved in N,N-dimethylformamide (3 ml), then treated with diisopropylethylamine (42 mg) and 1,1'-carbonyldiimidazole (34.2 mg). After 2 hours at room temperature, further diisopropylethylamine (42 mg) and 1,1'-carbonyldiimidazole (34.2 mg) were added. After 4 hours, the solution was diluted with pH 6.86 standard buffer solution and the solution was subjected to ODS column chromatography eluting with acetonitrile in water mixtures. Fractions containing the object compounds were pooled, evaporated and lyophilized separately to afford major object compound (24) (60 mg) and minor object compound (24) (55 mg) as white amorphous powders.

major object compound (24)

IR (KBr): 2935, 1658.5, 1635, 1444, 1259 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.9-1.05 (6H, m), 1.23-5.00

(43H, m), 3.22 (3H, s), 3.33 (2H, t, $J=6.6Hz$), 3.69

(3H, s), 6.76 (1H, d, $J=7.7Hz$), 6.81-6.86 (1H, m),

7.07 (1H, br s), 7.15 (2H, d, $J=9Hz$), 7.43 (1H, s),

7.68 (1H, s), 7.94-8.19 (6H, m)

MASS (m/z): 1417.4 (M^+-Na)

Elemental Analysis Calcd. for $C_{64}H_{81}N_{12}O_{21}S_2Na \cdot 5H_2O$:

C 50.19, H 5.99, N 10.97

35

Found: C 50.16, H 6.06, N 10.82

minor object compound (24)

IR (KBr): 2935, 2862, 1658.5, 1635, 1529, 1516, 1444,
1412, 1257 cm^{-1}

NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.98 (3H, d, $J=6.3\text{Hz}$), 1.05 (3H, d, $J=5.4\text{Hz}$), 1.2-4.9 (54H, complex m), 3.21 (3H, s), 3.31 (2H, t, $J=6.4\text{Hz}$), 6.7-6.75 (2H, m), 7.05 (1H, br s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.4-8.14 (8H, complex m)

MASS (m/z): 1486.5 (M^+)

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{90}\text{N}_{14}\text{O}_{20}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 51.18, H 6.44, N 12.29

Found: C 51.00, H 6.31, N 11.81

Example 25

To a solution of starting compound (25) (1.5 g) and (1,3-dioxy-2-oxo-4-cyclopenten-5-yl)-methoxycarbonyloxysuccinimide (0.47 g) in dimethylformamide (15 ml) was added diisopropylethylamine (0.302 ml) and stirred for 5 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried under reduced pressure.

The powder was added to pH 6.86 buffer and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 5-15% acetonitrile aq. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (25) (1.05 g).

IR (KBr): 3350, 1816.6, 1635.3, 1257.4 cm^{-1}

NMR (DMSO-d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.12 (3H, d, $J=5.8\text{Hz}$), 1.2-2.6 (17H, m), 2.13 (3H, s), 2.8-3.4 (7H, m), 3.21 (3H, s), 3.6-5.3 (28H, m), 6.72 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=8.2\text{Hz}$), 6.88 (1H, s),

7.13 (2H, d, J=8.6Hz), 7.25-7.8 (4H, m), 7.93 (2H, d, J=8.6Hz), 8.09 (4H, s), 8.73 (1H, s), 8.80 (1H, d, J=6.7Hz)

ESI MASS (m/z): 1453 ($M^+ - Na$)

5 Elemental Analysis Calcd. for C₆₄H₈₁N₁₀O₂₅S₂Na·5H₂O:
 C 49.04, H 5.85, N 8.94
 Found: C 48.98, H 5.75, N 9.05

Example 26

10 To a solution of starting compound (26) (0.2 g) and 4-
acetyloxymethoxycarbonyloxynitrobenzene (58.9 mg) in
dimethylformamide (1.5 ml) was added diisopropylethylamine
(0.04 ml) and stirred for 5 hours at ambient temperature.
The reaction mixture was pulverized with ethyl acetate. The
15 precipitate was collected by filtration and dried under
reduced pressure. The powder was added to pH 6.86 buffer and
subjected to column chromatography on ODS (YMC-gel ODS-AM-S-
50) (Trademark: prepared by Yamamura Chemical Lab.) and
eluted with 5-15% acetonitrile aq. The fractions containing
20 the object compound were combined and evaporated under
reduced pressure to remove acetonitrile. The residue was
lyophilized to give object compound (26) (26 mg).

IR (KBr): 3365.2, 1751.0, 1727.9, 1635.3, 1259.3 cm^{-1}

25 NMR (DMSO-d₆, δ): 0.96 (3H, d, J=6.6Hz), 1.12 (3H, d,
J=5.8Hz), 1.2-2.6 (17H, m), 2.04 (3H, s), 2.8-3.4
(7H, m), 3.21 (3H, s), 3.6-5.3 (26H, m), 5.61 (2H,
s), 6.70 (1H, d, J=8.2Hz), 6.77 (1H, d, J=8.2Hz),
6.96 (1H, s), 7.13 (2H, d, J=8.6Hz), 7.25-7.8 (4H,
m), 7.93 (2H, d, J=8.6Hz), 8.09 (4H, s), 8.73 (1H,
30 s), 8.80 (1H, d, J=6.7Hz)

ESI MASS (m/z): 1413 ($M^+ - Na$)

Example 27

A solution of 4-piperidone hydrochloride hydrate (28.4
35 mg) and succinic anhydride (18.5 mg) in DMF (2 ml) was

treated with diisopropylethylamine (23.9 mg) and aged for 3 hours at room temperature. To the resulting solution was added methanol (3 ml), DMF (1 ml), and after 30 minutes, acetic acid (27.7 mg), starting compound (31) (200 mg), and finally, sodium cyanoborohydride (12.6 mg). After 3 days at room temperature, ethyl acetate was added and the precipitate was collected, washed with ethyl acetate and dried. This solid was purified by ODS column chromatography (acetonitrile-water) to give object compound (27) (164 mg) as a white amorphous powder.

NMR (DMSO- d_6 + D₂O, δ): 0.96 (3H, d, J=6.6Hz), 1.12 (3H, d, J=5.6Hz), 1.2-4.9 (54H, complex m), 3.21 (3H, s), 3.31 (2H, t, J=6.4H), 6.7-6.8 (2H, m), 6.99 (1H, br s), 7.13 (2H, d, J=8.9H), 7.97 (2H, d, J=8.9Hz), 8.08 (4H, ABq, J=8.6Hz, separation of inner lines = 6.6Hz)

MASS (m/z): 1528.3 (M^+ +Na)

Elemental Analysis Calcd. for C₆₇H₉₀N₁₁O₂₃S₂Na·8H₂O:

C 48.81, H 6.48, N 9.34

Found: C 48.84, H 6.46, N 9.29

Example 28

To a solution of the starting compound (28) (200 mg) and molecular sieves (4A) (200 mg) in N,N-dimethylformamide (4 ml) was added methyl iodide (1 ml), and stirred for 4 days at ambient temperature. The reaction mixture was filtrated, and the filtrate was diluted in water, and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (28) (46 mg).

IR (KBr): 3355, 2935, 1664, 1627, 1446, 1405, 1375,
1257, 1178, 1083, 1047 cm^{-1}

NMR (DMSO-d_6 , δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.03 (3H, d,
 $J=6.2\text{Hz}$), 1.2-1.6 (8H, m), 1.6-2.6 (15H, m), 2.6-
3.8 (6H, m), 3.09 (9H, s), 3.21 (3H, s), 3.30 (4H,
t, $J=6.4\text{Hz}$), 3.8-4.2 (7H, m), 4.2-4.6 (4H, m), 4.6-
5.0 (2H, m), 5.28 (2H, m), 5.75 (1H, m), 6.69 (1H,
d, $J=8.2\text{Hz}$), 6.80 (1H, d, $J=8.2\text{Hz}$), 6.92 (1H, s),
7.14 (2H, d, $J=8.8\text{Hz}$), 7.35 (1H, d, $J=7.4\text{Hz}$), 7.5
(1H, m), 7.86 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.09
(4H, s), 8.32 (1H, s), 8.76 (1H, d, $J=6.8\text{Hz}$), 8.95
(1H, s)

MASS (m/z): 1363.4 ($M^+ + \text{Na}$)

Example 29

To a solution of starting compound (29) (0.2 g) and
ethyl bromoacetate (0.02 ml) in dimethylformamide (2 ml) was
added potassium carbonate (30.8 mg) and stirred for 24 hours
at ambient temperature. The reaction mixture was pulverized
with ethyl acetate. The precipitate was collected by
filtration and dried under reduced pressure. The powder was
added to 1N NaOH aq. (5 ml) and stirred for 1 hour at ambient
temperature. The reaction mixture was adjusted to pH 7 and
subjected to column chromatography on ODS (YMC-gel ODS-AM-S-
50) (Trademark: prepared by Yamamura Chemical Lab.) and
eluted with 30% acetonitrile aq. The fractions containing
the object compound were combined and evaporated under
reduced pressure to remove acetonitrile. The residue was
lyophilized to give object compound (29) (76 mg).

IR (KBr): 3353.6, 1631.5, 1444.4, 1257.4 cm^{-1}

ESI-MASS (m/z): 1355 ($M^+ - 1$)

Example 30

To a solution of starting compound (30) (0.1 g) and
ethyl bromoacetate (0.02 ml) in dimethylformamide (1 ml) was

added diisopropylethylamine (0.08 ml) and stirred for 24 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried under reduced pressure. The powder
5 was added to 1N NaOH aq. (5 ml) and stirred for 1 hour at ambient temperature. The reaction mixture was adjusted to pH 7 and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 30% acetonitrile aq. The fractions containing
10 the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (30) (48 mg).

IR (KBr): 3357.5, 1633.4, 1444.4, 1257.4 cm^{-1}

ESI-MASS (m/z): 1435 (M^+ +Na)

Example 31

A mixture of 4-[5-[4-[7-(cis-2,6-dimethylmorpholin-4-yl)heptyloxy]phenyl]isoxazol-3-yl]benzoic acid (100 mg), 1-hydroxybenzotriazole (41 mg) and 1-ethyl-3-(3'-
20 dimethylaminopropyl)carbodiimide hydrochloride (46.7 mg) in N,N-dimethylformamide (2 ml) was stirred for 30 minutes at ambient temperature. To the reaction mixture was added N,N-diisopropylethylamine (53.1 μl) and stirred for 40 minutes, then starting compound (31) (246.6 mg) was added and the
25 mixture was stirred for 4 hours. To the reaction mixture was added ethyl acetate (50 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude light-brown powder (400.3 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-
30 S-50 (Trademark: prepared by YMC CO., Ltd.)) (35% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (31).

IR (KBr): 3372.9, 1666.2, 1648.8, 1631.5, 1538.9,
1508.9, 1452.1, 1436.7, 1257.4 cm^{-1}

MASS (m/z): 1447.6 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{92}\text{N}_{10}\text{O}_{23}\text{S}\cdot 7\text{H}_2\text{O}$:

C 51.83, H 6.78, N 8.89

Found: C 52.10, H 6.67, N 8.91

Example 32

To a solution of starting compound (32) (0.1 g) and 1-ethoxy-1-imino-3-methoxypropane (38.7 mg) in dimethylformamide (1 ml) was added diisopropylethylamine (0.067 ml) and stirred for 20 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried under reduced pressure. The powder was added to pH 6.86 buffer and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 5-50% acetonitrile aq. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (32) (42 mg).

IR (KBr): 3353.6, 1635.3, 1257.4 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.98 (3H, d, $J=6.6\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.2-2.6 (19H, m), 2.8-3.4 (9H, m), 3.21 (3H, s), 3.6-5.3 (26H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=8.2\text{Hz}$), 7.00 (1H, s), 7.13 (2H, d, $J=8.6\text{Hz}$), 7.25-7.8 (3H, m), 7.96 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=8.9\text{Hz}$), 8.11 (2H, d, $J=8.9\text{Hz}$), 8.70 (1H, s), 8.85 (1H, d, $J=6.7\text{Hz}$)

MASS (m/z): 1383 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{85}\text{N}_{11}\text{O}_{21}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 48.71, H 6.66, N 10.08

Found: C 48.50, H 6.50, N 9.96

Example 33

To a solution of starting compound (33) (0.1 g) and 2-carbamoyl-1-ethoxy-1-iminopropane (38.5 mg) in dimethylformamide (1 ml) was added diisopropylethylamine (0.067 ml) and stirred for 20 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried under reduced pressure. The powder was added to pH 6.86 buffer and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 5-50% acetonitrile aq. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (33) (48 mg).

IR (KBr): 1658.5, 1635.3, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.6\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.2-2.6 (17H, m), 2.8-3.4 (7H, m), 3.21 (3H, s), 3.6-5.3 (28H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=8.2\text{Hz}$), 7.00 (1H, s), 7.13 (2H, d, $J=8.6\text{Hz}$), 7.32 (1H, s), 7.25-7.8 (4H, m), 7.96 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=8.9\text{Hz}$), 8.11 (2H, d, $J=8.9\text{Hz}$), 8.70 (1H, s), 8.85 (1H, d, $J=6.7\text{Hz}$)

ESI-MASS (m/z): 1382 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{82}\text{N}_{12}\text{O}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 48.53, H 6.41, N 11.13

Found: C 48.50, H 6.39, N 10.92

Example 34

A mixture of starting compound (34) (50 mg), N,N-diisopropylethylamine (6.70 μl) and zeolite synthetic A-4 powder (50 mg) in N,N-dimethylformamide (0.5 ml) was stirred for 30 minutes at ambient temperature. To the mixture was added acetic anhydride (3.63 μl) and stirred for 2 hours. The zeolite synthetic A-4 powder was filtered off, and to the filtrate was added ethyl acetate (100 ml). The resulting

precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (48.7 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (25% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (34) (31.5 mg).

IR (KBr): 3353.6, 1658.5, 1635.3, 1546.6, 1531.2, 1517.7, 1444.4, 1259.3 cm^{-1}

NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d, $J=5.9\text{Hz}$), 1.2-5.5 (55H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 6.96 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.3-7.8 (4H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 7.9-9.0 (7H, m)

MASS (m/z): 1339.3 ($\text{M}^- - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{79}\text{N}_{10}\text{NaO}_{21}\text{S}_3 \cdot 10\text{H}_2\text{O}$:

C 46.69, H 6.46, N 9.07

Found: C 46.46, H 6.11, N 8.95

Example 35

A solution of starting compound (35) (500 mg) in water (20 ml) and 1N-sodium hydroxide (1.15 μl) was treated dropwise with a solution of allyloxycarbonyl chloride (49 μl) in tetrahydrofuran (1 ml). After 1 hour, the solution was diluted with water and purified by ODS column chromatography eluting with acetonitrile-water mixtures. Product-containing fractions were pooled, evaporated to remove organic solvent and lyophilized to give object compound (35) (350 mg) as a white amorphous powder.

IR (KBr): 2935, 1664, 1633, 1610, 1527, 1442.5, 1412, 1383, 1348, 1257, 1178, 1113, 1088, 1045 cm^{-1}

NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.2-5.1 (53H, complex m), 3.21 (3H, s), 3.31 (2H, t, $J=6.4\text{Hz}$), 5.12-5.29 (2H, m), 5.8-

6.0 (1H, m), 6.70-6.80 (2H, m), 6.99 (1H, br s),
7.14 (2H, d, J=8.8Hz), 7.98 (2H, d, J=8.8Hz), 8.09
(4H, s)

MASS (m/z): 1381.3 (M^+ -Na)

5 Elemental Analysis Calcd. for $C_{62}H_{81}N_{10}O_{22}S_2Na \cdot 5H_2O$:
C 49.79, H 6.13, N 9.37
Found: C 49.79, H 6.07, N 9.30

Example 36

10 To a solution of starting compound (36) (100 mg) in N,N-
dimethylformamide (1 ml) was added sulfur trioxide pyridine
complex (61.2 mg) and stirred for 2 days at ambient
temperature. To the reaction mixture was added ethyl acetate
(30 ml), and the resulting precipitate was collected by
15 filtration and washed with diisopropyl ether to give a crude
white powder. The crude powder was purified by column
chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark:
prepared by YMC Co., Ltd.)) (20% acetonitrile aqueous
solution). The fractions containing the object compound were
20 combined, and evaporated under reduced pressure to remove
acetonitrile. The residue was lyophilized to give object
compound (36) (12.7 mg).

IR (KBr): 3446.2, 1648.8, 1633.4, 1540.8, 1515.8,
1450.2, 1442.5, 1257.4 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.5Hz), 1.0-5.4 (56H,
m), 6.6-6.8 (2H, m), 6.9-7.1 (1H, m), 7.13 (2H, d,
J=8.8Hz), 7.97 (2H, d, J=8.8Hz), 8.08 (4H, s), 7.3-
9.0 (7H, m)

MASS (m/z): 1399.3 (M^- -1)

Example 37

A mixture of starting compound (37) (100 mg), N,N-
diisopropylethylamine (14.7 μ l), zeolite synthetic A-4 powder
(400 mg) and N,N-dimethylformamide dimethyl acetal (15.3 μ l)
35 in N,N-dimethylformamide (1 ml) was stirred for 40 minutes at

ambient temperature. To the reaction mixture was added N,N-diisopropylethylamine (1.5 μ l) and N,N-dimethylformamide dimethyl acetal (1.5 μ l), the mixture was stirred for 1 hour at ambient temperature, and ethyl acetate (50 ml) was added, and the resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (72.2 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (40% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (37) (27.9 mg).

IR (KBr): 3359.4, 1710.6, 1648.8, 1631.5, 1538.9, 1513.8, 1442.5, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.0-5.4 (62H, m), 6.6-6.9 (2H, m), 6.99 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.3-7.9 (3H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.0-8.2 (4H, m), 8.3-9.2 (4H, m)

MASS (m/z): 1352.5 ($M^- - 1$)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{83}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 49.02, H 6.41, N 10.31

Found: C 49.20, H 6.35, N 10.27

Example 38

To a solution of the starting compound (38) (100 mg) in N,N-dimethylformamide (1 ml) was added S,S'-dimethyl N-cyanodithioiminocarbonate (113 mg) and diisopropyl ethyl amine (0.2 ml), and stirred for 2 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate and washed by diisopropyl ether. The precipitate was filtered and dried to give the object compound (38) (111 mg).

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.0-1.6 (14H, m), 1.6-3.9 (25H, m), 3.21 (3H, s), 3.9-4.3 (7H, m), 4.43 (2H, m), 4.5-4.7 (2H, m), 4.88 (2H, d,

J=5.7Hz), 5.0-5.3 (4H, m), 6.71 (1H, d, J=8.2Hz),
6.78 (1H, d, J=8.2Hz), 6.97 (1H, s), 7.13 (2H, d,
J=8.8Hz), 7.50 (1H, d, J=8.5Hz), 7.63 (1H, m), 7.7
(1H, m), 7.97 (2H, d, J=8.8Hz), 8.09 (4H, s), 8.12
(1H, m), 8.71 (1H, s), 8.78 (1H, d, J=6.4Hz)

MASS (m/z): 1395.3 ($M^{+}-1$)

Example 39

To a solution of the starting compound (39) (96 mg) in
water (1 ml) was added a solution of ammonia in methanol (1
ml), and stirred for 2 days at ambient temperature. The
reaction mixture was diluted in water, and subjected to
column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark:
prepared by Yamamura Chemical Lab.)) eluting with 20%
acetonitrile aqueous solution. The fractions containing the
object compound were combined, and evaporated under reduced
pressure to remove acetonitrile. The residue was lyophilized
to give the object compound (39) (39 mg).

IR (KBr): 3351, 2935, 1635, 1567, 1533, 1517, 1444,
1415, 1257, 1178, 1087, 1047 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, J=6.7Hz), 1.13 (3H, d,
J=5.7Hz), 1.2-1.6 (11H, m), 1.6-2.6 (10H, m), 2.90
(1H, m), 3.20 (1H, m), 3.21 (3H, s), 3.30 (4H, t,
J=6.4Hz), 3.3-4.6 (14H, m), 4.6-4.8 (2H, m), 4.87
(1H, d, J=5.7Hz), 5.06 (1H, d, J=7.2Hz), 5.2 (4H,
m), 6.71 (1H, d, J=8.2Hz), 6.78 (1H, d, J=8.2Hz),
6.7 (3H, m), 6.97 (1H, s), 7.13 (2H, d, J=8.8Hz),
7.46 (1H, d, J=8.8Hz), 7.65 (2H, m), 7.97 (2H, d,
J=8.8Hz), 8.09 (4H, s), 8.13 (1H, m), 8.71 (1H, s),
8.84 (1H, d, J=7.7Hz)

MASS (m/z): 1364.4 ($M^{+}-\text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{78}\text{N}_{13}\text{NaO}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 47.02, H 6.18, N 11.88

Found: C 47.15, H 5.89, N 11.82

Example 40

To a solution of the starting compound (40) (100 mg) in acetonitrile (1 ml) and water (1 ml) was added formaline (35% aqueous) (67 μ l), and stirred for 30 minutes at ambient temperature. To a solution of the reaction mixture was added sodium cyanoborohydride (48 mg) and stirred for 5 hours. The reaction mixture was diluted in water, and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (40) (27 mg).

IR (KBr): 3355, 2937, 1658, 1633, 1533, 1517, 1444, 1257, 1178, 1087, 1045 cm^{-1}

NMR (DMSO-d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.3-2.6 (30H, m), 2.6-3.0 (4H, m), 3.21 (3H, s), 3.0-4.1 (11H, m), 4.22 (2H, m), 4.4 (4H, m), 4.80 (3H, m), 4.9 (2H, m), 5.17 (2H, m), 5.24 (1H, d, $J=5.7\text{Hz}$), 6.69 (1H, d, $J=8.2\text{Hz}$), 6.76 (1H, d, $J=8.2\text{Hz}$), 6.99 (1H, s), 7.05 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.41 (2H, d, $J=9.1\text{Hz}$), 7.85 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.10 (4H, s), 8.70 (1H, m), 8.72 (1H, s), 8.87 (1H, m)

MASS (m/z): 1365.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 50.06, H 6.80, N 9.27

Found: C 49.95, H 6.38, N 9.21

Example 41

To a solution of the starting compound (41) (100 mg) and potassium carbonate (53 mg) in N,N -dimethylformamide (1 ml) was added 1,5-dibromopentane (13 μ l), and stirred for 3 days at ambient temperature. The reaction mixture was filtrated, and the filtrate was diluted in water, and subjected to

column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (41) (38 mg).

IR (KBr): 3353, 2935, 1658, 1635, 1546, 1529, 1517, 1444, 1257, 1083, 1047 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.7\text{Hz}$), 1.3-1.6 (8H, m), 1.6-2.4 (15H, m), 2.4-3.0 (6H, m), 3.21 (3H, s), 3.0-4.2 (11H, m), 4.23 (2H, m), 4.43 (4H, m), 4.80 (3H, m), 4.95 (2H, d, $J=6.2\text{Hz}$), 5.1-5.3 (3H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=8.2\text{Hz}$), 6.99 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.43 (2H, m), 7.83 (1H, d, $J=7.2\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.10 (4H, s), 8.60 (1H, m), 8.71 (1H, s), 8.87 (1H, d, $J=7.2\text{Hz}$)

MASS (m/z): 1325.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{92}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 48.97, H 6.71, N 9.52

Found: C 48.97, H 6.32, N 9.63

Example 42

To a solution of the starting compound (42) (200 mg) and molecular sieves (4A) (200 mg) in N,N-dimethylformamide (4 ml) was added cyanogen bromide (80 mg), and stirred for 5 hours at ambient temperature. The reaction mixture was filtrated, and the filtrate was diluted in water, and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (42) (3.8 mg).

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d,

J=5.7Hz), 1.2-1.6 (8H, m), 1.6-4.5 (30H, m), 2.79 (3H, s), 3.21 (3H, s), 4.7 (2H, m), 4.85 (2H, d, J=6.0Hz), 5.07 (2H, m), 5.2 (3H, m), 6.69 (2H, m), 6.95 (1H, s), 7.14 (2H, d, J=8.8Hz), 7.46 (1H, m), 7.64 (2H, m), 7.97 (2H, d, J=8.8Hz), 8.09 (4H, s), 8.07 (1H, d, J=7.8Hz), 8.57 (1H, d, J=7.8Hz), 8.27 (1H, m), 8.68 (1H, m), 8.72 (1H, s)

MASS (m/z): 1336.3 ($M^+ - 1$)

10 Example 43

A solution of starting compound (43) (100 mg) in N,N-dimethylformamide (2 ml) was treated with 1,1'-carbonyldiimidazole (16.2 mg) and diisopropylethylamine (10.9 mg). After 20 hours, a further 3.7 mg of 1,1-carbonyldiimidazole was added. After a further 1 hour, the mixture was diluted with water and purified by ODS column chromatography eluting with acetonitrile-water mixtures and product-containing fractions lyophilized to afford 80.8 mg of object compound (43) as a white amorphous powder.

IR (KBr): 2935, 2864, 1658.5, 1637, 1529, 1518, 1444, 1257 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.93-1.07 (6H, m), 1.20-4.5 (37H, m), 3.21 (3H, s), 3.31 (2H, t, J=6.4Hz), 4.07 (2H, t, J=6.3Hz), 4.81 (1H, m), 4.99 (1H, d, J=4Hz), 6.71 (1H, d, J=8.2Hz), 6.78-6.83 (1H, m), 6.98 (1H, d, J=1.7Hz), 7.13 (2H, d, J=8.9Hz), 7.97 (2H, d, J=8.9Hz), 8.02-8.13 (4H, m)

MASS (m/z): 1323.2 ($M^+ - Na$)

Elemental Analysis Calcd. for $C_{59}H_{75}N_{10}O_{21}S_2N_9 \cdot 6H_2O$:

C 48.39, H 6.06, N 9.56

Found: C 48.37, H 6.00, N 9.61

The following compound was obtained according to a similar manner to that of Example 43.

Example 44

IR (KBr): 3352, 2935, 2864, 1635, 1547, 1516, 1444,
1255, 1174, 1045 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.95 (3H, d, $J=6.9\text{Hz}$), 1.03 (3H,
5 d, $J=5.9\text{Hz}$), 1.20-5.12 (39H, m), 3.21 (3H, s), 3.31
(2H, t, $J=6.4\text{Hz}$), 4.07 (2H, t, $J=6.1\text{Hz}$), 6.72 (1H,
d, $J=8.2\text{Hz}$), 6.82 (1H, dd, $J=8.2, 1.7\text{Hz}$), 6.99 (1H,
d, $J=1.7\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.98 (2H, d,
 $J=8.9\text{Hz}$), 8.08 (4H, m)

10 MASS (m/z): 1339.2 ($\text{M}^+ - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{75}\text{N}_{10}\text{O}_{20}\text{S}_3\text{Na} \cdot 6\text{H}_2\text{O}$:

C 48.16, H 5.96, N 9.52

Found: C 48.01, H 5.74, N 9.43

15 Example 45

A mixture of starting compound (45) (220 mg) and 1N
sodium hydroxide aqueous solution (30 ml) was stirred for 1
hour at ambient temperature. The reaction mixture was
adjusted to pH 9 with 1N hydrochloric acid, and purified by
20 column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark:
prepared by YMC Co., Ltd.)) (20% acetonitrile aqueous
solution). The fractions containing the object compound were
combined, and evaporated under reduced pressure to remove
acetonitrile. The residue was lyophilized to give object
25 compound (45).

IR (KBr): 3382.5, 1658.5, 1635.3, 1444.4, 1257.4,
1087.7, 1045.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.9\text{Hz}$), 1.11 (3H, d,
 $J=5.0\text{Hz}$), 1.2-5.4 (64H, m), 6.68 (1H, d, $J=8.1\text{Hz}$),
30 6.78 (1H, d, $J=8.0\text{Hz}$), 6.92 (1H, d, $J=1.8\text{Hz}$), 7.13
(2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.07 (4H,
s), 7.3-9.0 (6H, m)

MASS (m/z): 1411.4 ($\text{M}^- - \text{Na}$)

35 The following compounds were obtained according to a

similar manner to that of Example 45.

Example 46

major object compound (46)

5 IR (KBr): 3353.6, 1658.5, 1635.3, 1546.6, 1529.3,
1517.7, 1444.4, 1257.4 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.3\text{Hz}$), 1.2-5.4 (70H, m), 6.68 (1H, d, $J=8.2\text{Hz}$),
6.76 (1H, d, $J=9.7\text{Hz}$), 6.92 (1H, s), 7.13 (2H, d,
10 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.04 (2H, d,
 $J=9.3\text{Hz}$), 8.10 (2H, d, $J=9.0\text{Hz}$), 7.3-9.0 (6H, m)
MASS (m/z): 1453.4 (M^- -Na)
Elemental Analysis Calcd. for $\text{C}_{67}\text{H}_{93}\text{N}_{10}\text{NaO}_{22}\text{S}_2 \cdot 9\text{H}_2\text{O}$:
C 49.08, H 6.82, N 8.54
15 Found: C 49.20, H 6.72, N 8.56

minor object compound (46)

IR (KBr): 3353.6, 1658.5, 1635.3, 1567.8, 1550.5,
1533.1, 1517.7, 1444.4, 1407.8, 1257.4 cm^{-1}
20 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.1-5.4 (88H,
m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=9.8\text{Hz}$),
6.90 (1H, s), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d,
 $J=8.8\text{Hz}$), 8.07 (4H, s), 7.3-9.0 (6H, m)
MASS (m/z): 1631.4 (M^- -Na)
25 Elemental Analysis Calcd. for $\text{C}_{76}\text{H}_{108}\text{N}_{10}\text{Na}_2\text{O}_{24}\text{S}_2 \cdot 11\text{H}_2\text{O}$:
C 49.24, H 7.07, N 7.55
Found: C 49.22, H 6.93, N 7.57

Example 47

30

deleted

35

5

deleted

10

15

Example 48

20 A mixture of starting compound (48) (100 mg), N,N-diisopropylethylamine (13.4 μ l) and zeolite synthetic A-4 powder (100 mg) in N,N-dimethylformamide (1 ml) was stirred for 30 minutes at ambient temperature. The mixture was cooled to 0°C and treated with methanesulfonyl chloride (6 μ l) and stirred for 30 minutes at ambient temperature. The
25 mixture was then treated with further methanesulfonyl chloride (6 μ l) and stirred for 30 minutes at ambient temperature. To the mixture was added N,N-diisopropylethylamine (13.4 μ l) and stirred for 15 minutes at ambient temperature. The mixture was treated with
30 methanesulfonyl chloride (6 μ l) and stirred for 30 minutes at ambient temperature. To the mixture was added N,N-diisopropylethylamine (13.4 μ l) and stirred for 15 minutes at ambient temperature. The zeolite synthetic A-4 powder was filtered off, and to the filtrate was added ethyl acetate
35 (100 ml). The resulting precipitate was collected by

filtration and washed with diisopropyl ether to give a crude powder. The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (25% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (48) (30.0 mg).

IR (KBr): 3430.7, 1658.5, 1635.3, 1444.4, 1259.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d, $J=5.9\text{Hz}$), 1.2-5.5 (55H, m), 6.6-6.9 (3H, m), 6.97 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.3-7.8 (3H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.09 (4H, s), 8.0-9.0 (3H, m)

MASS (m/z): 1375.3 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{79}\text{N}_{10}\text{NaO}_{22}\text{S}_3 \cdot 7\text{H}_2\text{O}$:

C 46.45, H 6.14, N 9.18

Found: C 46.26, H 6.11, N 9.01

The following compounds [Examples 49 to 52] were obtained according to a similar manner to that of Example 48.

Example 49

IR (KBr): 3380.6, 1666.2, 1648.8, 1631.5, 1538.9, 1513.8, 1450.2, 1450.2, 1261.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d, $J=5.9\text{Hz}$), 1.2-5.5 (60H, m), 6.4-6.6 (1H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=9.8\text{Hz}$), 6.96 (1H, s), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.3-8.2 (4H, m), 7.93 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=9.0\text{Hz}$), 8.11 (2H, d, $J=8.9\text{Hz}$), 8.5-9.0 (2H, m)

MASS (m/z): 1410.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{84}\text{N}_{11}\text{NaO}_{22}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 47.93, H 6.38, N 9.76

Found: C 48.05, H 6.25, N 9.56

Example 50

IR (KBr): 3363.2, 1666.2, 1648.8, 1631.5, 1540.8,
1513.8, 1450.2, 1442.5, 1257.4 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d,
 $J=5.9\text{Hz}$), 1.2-5.5 (58H, m), 6.1-6.3 (1H, m), 6.71
(1H, d, $J=18.1\text{Hz}$), 6.78 (1H, d, $J=10.0\text{Hz}$), 6.96
(1H, s), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.4-7.9 (4H, m),
7.97 (2H, d, $J=8.7\text{Hz}$), 8.06 (2H, d, $J=10.4\text{Hz}$), 8.11
10 (2H, d, $J=9.0\text{Hz}$), 8.6-8.8 (2H, m)

MASS (m/z): 1368.4 ($\text{M}^- - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{82}\text{N}_{11}\text{NaO}_{21}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 47.13, H 6.48, N 9.91

Found: C 47.36, H 6.24, N 9.86

Example 51

IR (KBr): 3359.4, 1666.2, 1648.8, 1631.5, 1540.8,
1513.8, 1450.2, 1442.5, 1257.4 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.8-1.1 (9H, m), 1.17 (3H, d,
 $J=6.0\text{Hz}$), 1.2-5.5 (56H, m), 6.0-6.2 (1H, m), 6.71
(1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 6.96 (1H, d,
 $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.4-7.9 (4H, m),
7.97 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d, $J=9.3\text{Hz}$), 8.10
(2H, d, $J=9.0\text{Hz}$), 8.6-8.8 (2H, m)

25 MASS (m/z): 1396.5 ($\text{M}^- - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{11}\text{NaO}_{21}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 48.36, H 6.57, N 9.85

Found: C 48.50, H 6.34, N 9.82

Example 52

30 IR (KBr): 3392.2, 1631.5, 1504.8, 1515.8, 1442.5,
1257.4 cm^{-1}

35 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d,
 $J=5.7\text{Hz}$), 1.2-5.5 (60H, m), 5.9-6.1 (1H, m), 6.71
(1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=10.0\text{Hz}$), 6.96 (1H,

s), 7.13 (2H, d, J=8.8Hz), 7.3-7.9 (4H, m), 7.97 (2H, d, J=8.8Hz), 8.0-8.2 (4H, m), 8.6-8.8 (2H, m)

MASS (m/z): 1394.4 (M^- -Na)

5 Example 53

To a mixture of starting compound (53) (100 mg) and zeolite synthetic A-4 powder (100 mg) in N,N-dimethylformamide (1 ml) was added propane sultone (9.4 mg) and stirred for 3 days 7 hours at ambient temperature. To the reaction mixture was added ethyl acetate (20 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (104.3 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (20% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (53) (34.2 mg).

IR (KBr): 3372.9, 1658.5, 1635.3, 1546.6, 1529.3, 1517.7, 1444.4, 1255.4, 1178.3, 1045.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.6Hz), 1.13 (3H, d, J=5.8Hz), 1.2-5.5 (60H, m), 6.71 (1H, d, J=8.2Hz), 6.77 (1H, d, J=10.0Hz), 6.95 (1H, s), 7.13 (2H, d, J=8.9Hz), 7.97 (2H, d, J=8.7Hz), 8.09 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1419.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{83}\text{N}_{10}\text{NaO}_{23}\text{S}_3 \cdot 8\text{H}_2\text{O}$:

C 46.15, H 6.28, N 8.82

Found: C 46.11, H 6.04, N 8.74

The following compounds [Examples 54 to 56] were obtained according to a similar manner to that of Example 53.

Example 54

IR (KBr): 3355.5, 2935.1, 1635.3, 1529.3, 1517.7,
1444.4, 1257.4, 1178.3, 1045.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.12 (3H, d,
 $J=5.3\text{Hz}$), 1.2-5.4 (62H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.78 (1H, d, $J=9.5\text{Hz}$), 6.96 (1H, s), 7.13 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.05 (2H, d,
 $J=8.8\text{Hz}$), 8.12 (2H, d, $J=8.5\text{Hz}$), 7.3-9.0 (6H, m)

MASS (m/z): 1455.3 (M^{-1})

Example 55

IR (KBr): 3369.0, 1633.4, 1533.1, 1517.7, 1444.4,
1413.6, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.14 (3H, d,
 $J=5.7\text{Hz}$), 1.2-5.4 (58H, m), 6.6-6.9 (2H, m), 6.94
(1H, s), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d,
 $J=8.8\text{Hz}$), 8.08 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1391.2 (M^{-1})

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{81}\text{N}_{10}\text{NaO}_{22}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 47.65, H 6.36, N 9.11

Found: C 47.52, H 6.10, N 8.84

Example 56

IR (KBr): 3363.2, 1666.2, 1648.8, 1631.5, 1538.9,
1513.8, 1450.2, 1442.5, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.12 (3H, d,
 $J=5.6\text{Hz}$), 1.2-5.6 (60H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.77 (1H, d, $J=9.1\text{Hz}$), 6.97 (1H, s), 7.13 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.06 (2H, d,
 $J=8.6\text{Hz}$), 8.13 (2H, d, $J=8.7\text{Hz}$), 7.3-9.0 (6H, m)

MASS (m/z): 1457.4 (M^{-1})

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{83}\text{N}_{10}\text{NaO}_{24}\text{S}_3 \cdot 9\text{H}_2\text{O}$:

C 45.18, H 6.28, N 8.64

Found: C 45.14, H 6.11, N 8.52

The following compounds [Examples 57 to 58] were obtained according to a similar manner to that of Example 18.

Example 57

5 IR (KBr): 1670, 1632, 1535, 1518, 1443 cm^{-1}
NMR (DMSO-d_6 + D_2O , δ): 0.94 (3H, d, $J=6.70\text{Hz}$), 1.10
(3H, d, $J=5.86\text{Hz}$), 1.35 (9H, s), 1.45-1.95 (6H, m),
2.10-2.40 (2H, m), 2.80-3.45 (7H, m), 3.60-4.80
(15H, m), 5.05-5.40 (2H, m), 5.70-6.05 (1H, m),
10 6.74 (1H, d, $J=8.18\text{Hz}$), 6.82 (1H, d, $J=10.2\text{Hz}$),
7.06 (1H, s)
ESI MASS (m/z)(Positive): 1135.2 ($\text{M}^+ + \text{Na}$)
Elemental Analysis Calcd. for $\text{C}_{44}\text{H}_{65}\text{N}_8\text{O}_{22}\text{SNa}\cdot 4\text{H}_2\text{O}$:
C 44.59, H 6.21, N 9.45
15 Found: C 44.55, H 6.37, N 9.39

Example 58

IR (KBr): 3344, 2925.5, 2854, 1664, 1635, 1529, 1518,
1446, 1277, 1252, 1171, 1086, 1045 cm^{-1}
20 NMR (DMSO-d_6 + D_2O , δ): 0.82-0.88 (3H, m), 0.97 (3H, d,
 $J=6.6\text{Hz}$), 1.08 (3H, d, $J=5.5\text{Hz}$), 1.37 (9H, s), 1.5-
4.80 (57H, complex m), 6.71-6.79 (2H, m), 7.00 (1H,
br s)
MASS (m/z): 1227.4 ($\text{M}^+ - \text{Na}$)
25 Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{91}\text{N}_8\text{O}_{20}\text{SNa}\cdot 5\text{H}_2\text{O}$:
C 50.14, H 7.59, N 8.35
Found: C 49.93, H 7.51, N 8.31

Example 59

30 A mixture of 4-[5-[4-(6-methoxyhexyloxy)phenyl]-
isoxazol-3-yl]benzoic acid (100 mg), 1-hydroxybenzotriazole
(51.3 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
hydrochloride (58.2 mg) and N,N-diisopropylethylamine (66.1
 μl) in N,N-dimethylformamide (2 ml) was stirred for 4.5
35 hours. To the reaction mixture was added starting compound

(59) (246.6 mg) and stirred for overnight. To the reaction mixture was added ethyl acetate (100 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give object compound (59) as a crude white powder (406.7 mg), that was used crude in the next reaction.

The following compounds [Example 60 to 62] were obtained according to a similar manner to that of Example 59.

Example 60

The object compound (60) was used directly in the next reaction without purification.

Example 61

The object compound (61) was used directly in the next reaction without purification.

Example 62

The object compound (62) was used directly in the next reaction without purification.

The following compounds [Examples 63 to 77] were obtained according to a similar manner to that of Preparation 84.

Example 63

IR (KBr): 3369.0, 1631.5, 1538.9, 1513.8, 1442.5,
1257.4 cm^{-1}

NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.11 (3H, d, $J=5.4\text{Hz}$), 1.2-5.6 (70H, m), 6.71 (1H, d, $J=8.3\text{Hz}$), 6.77 (1H, d, $J=9.6\text{Hz}$), 6.99 (1H, s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.6\text{Hz}$), 8.04 (2H, d, $J=8.5\text{Hz}$), 8.11 (2H, d, $J=8.3\text{Hz}$), 7.3-9.0 (6H, m)

ESI MASS (m/z): 1442.6 (M^{-1})

Elemental Analysis Calcd. for $C_{65}H_{93}N_{11}O_{22}S_2 \cdot 7H_2O$:

C 49.70, H 6.87, N 9.81

Found: C 49.43, H 6.71, N 9.71

5 Example 64

IR (KBr): 1633, 1606, 1527, 1518, 1466 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7Hz$), 1.11 (3H, d, $J=5.6Hz$), 1.2-2.5 (18H, m), 2.7-4.6 (34H, m), 4.6-5.4 (8H, m), 6.7-7.2 (5H, m), 7.3-7.6 (2H, m), 7.6-7.85 (4H, m), 7.95 (4H, s), 8.2-8.4 (1H, m), 8.6-8.75 (1H, m), 8.80 (1H, s)

MASS (m/z): 1407 ($M^+ + 1$)

Example 65

IR (KBr): 3363.2, 1666.2, 1648.8, 1631.5, 1538.9, 1508.1, 1452.1, 1436.7, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8Hz$), 1.11 (3H, d, $J=5.7Hz$), 1.2-5.6 (53H, m), 6.71 (1H, d, $J=8.1Hz$), 6.7-6.9 (1H, m), 7.01 (1H, d, $J=1.6Hz$), 7.13 (2H, d, $J=8.9Hz$), 7.45 (1H, d, $J=8.3Hz$), 7.55 (1H, s), 7.85 (2H, d, $J=8.7Hz$), 7.6-7.9 (2H, m), 7.99 (2H, d, $J=8.8Hz$), 8.05 (2H, d, $J=8.9Hz$), 8.32 (1H, d, $J=7.3Hz$), 8.71 (1H, s), 8.87 (1H, d, $J=7.5Hz$)

MASS (m/z): 1266.4 ($M^- - 1$)

Elemental Analysis Calcd. for $C_{58}H_{77}N_9O_{21}S \cdot 8H_2O$:

C 49.32, H 6.64, N 8.92

Found: C 49.42, H 6.43, N 8.88

Example 66

IR (KBr): 3490, 3463, 3424, 3357, 2935, 1633, 1542, 1519 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.6Hz$), 1.12 (3H, d, $J=5.4Hz$), 1.22-1.35 (6H, m), 1.35-2.40 (15H, m), 2.80-3.10 (3H, m), 3.18 (3H, s), 3.25 (3H, t, $J=6.4Hz$), 3.45-3.60 (3H, m), 3.65-4.60 (15H, m),

4.70-5.30 (8H, m), 6.70-6.80 (2H, m), 7.00 (1H, br s), 7.40-7.75 (3H, m), 8.00-8.40 (3H, m), 8.46 (2H, d, J=8.4Hz), 8.50-9.00 (2H, m)

MASS (m/z)(API-ES-negative): 1332 ($M^{+}+1$)

5 Elemental Analysis Calcd. for $C_{58}H_{38}N_{10}O_{22}S_2 \cdot 5H_2O$:
C 49.00, H 6.19, N 9.85
Found: C 49.20, H 6.15, N 9.69

Example 67

10 IR (KBr): 3457, 3425, 3400, 3365, 2931, 1639, 1537,
1518 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.4Hz), 1.20-1.35 (12H, m), 1.35-1.70 (6H, m), 1.70-2.40 (7H, m), 2.80-3.10 (3H, m), 3.17 (3H, s), 15 3.26 (3H, t, J=6.4Hz), 3.30-3.50 (3H, m), 3.65-4.10 (6H, m), 4.10-4.60 (7H, m), 4.65-5.40 (8H, m), 6.60-6.80 (2H, m), 7.00 (1H, br s), 7.30-7.80 (6H, m), 8.05-8.40 (7H, m), 8.47 (2H, d, J=8.4Hz), 8.71 (1H, br s), 8.93 (1H, m)

20 MASS (m/z)(API-ES Negative): 1360 ($M^{+}+1$)
Elemental Analysis Calcd. for $C_{60}H_{82}N_{10}O_{22}S_2 \cdot 6H_2O$:
C 49.08, H 6.41, N 9.54
Found: C 48.88, H 6.41, N 9.47

25 Example 68

IR (KBr): 3457, 3424, 3400, 3367, 2935, 1637, 1509,
1261 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.4Hz), 1.20-1.50 (9H, m), 1.60-2.45 (9H, m), 30 3.21 (3H, s), 3.30 (2H, t, J=6.5Hz), 3.40-3.90 (6H, m), 3.90-4.55 (12H, m), 4.60-5.80 (6H, m), 6.72 (1H, d, J=8.1Hz), 6.74 (1H, dd, J=1.5 and 8.4Hz), 7.00 (1H, d, J=1.5Hz), 7.20 (2H, d, J=8.9Hz), 7.40-7.90 (4H, m), 8.00-8.40 (6H, m), 8.94 (1H, m)

35 MASS (m/z)(API-ES-Negative): 1284 ($M^{+}+1$)

Elemental Analysis Calcd. for $C_{58}H_{78}N_{10}O_{21}S \cdot 7H_2O$:

C 49.40, H 6.53, N 9.94

Found: C 49.17, H 6.36, N 9.74

5 Example 69

IR (KBr): 3458, 3423, 3398, 3367, 2931, 1637, 1508,
1259 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7Hz$), 1.12 (3H, d,
J=5.5Hz), 1.20-1.60 (12H, m), 1.65-2.45 (9H, m),
2.80-3.15 (3H, m), 3.20 (3H, s), 3.29 (3H, t,
J=6.5Hz), 3.80-4.50 (17H, m), 4.60-5.30 (8H, m),
6.71 (1H, d, $J=8.2Hz$), 6.69-6.80 (1H, m), 7.00 (1H,
br s), 7.20 (2H, d, $J=8.9Hz$), 7.30-7.90 (7H, m),
8.05-8.40 (8H, m), 8.60-9.00 (2H, m)

MASS (m/z)(API-ES-Negative): 1312 ($M^+ + 1$)

Elemental Analysis Calcd. for $C_{60}H_{82}N_{10}O_{21}S \cdot 6H_2O$:

C 50.74, H 6.62, N 9.87

Found: C 50.48, H 6.56, N 9.60

20 Example 70

IR (KBr): 3372.9, 1664.3, 1635.3, 1361.5, 1444.4,
1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8Hz$), 1.12 (3H, d,
J=5.8Hz), 1.2-5.3 (55H, m), 6.71 (1H, d, $J=8.1Hz$),
6.7-6.9 (1H, m), 7.00 (1H, d, $J=1.6Hz$), 7.12 (2H,
d, $J=8.9Hz$), 7.45 (1H, d, $J=8.6Hz$), 7.54 (1H, s),
7.6-7.8 (2H, m), 7.85 (2H, d, $J=8.7Hz$), 7.99 (2H,
d, $J=8.7Hz$), 8.05 (2H, d, $J=8.9Hz$), 8.25 (1H, d,
J=6.7Hz), 8.81 (1H, d, $J=7.4Hz$)

MASS (m/z): 1280.4 ($M^- - 1$)

Elemental Analysis Calcd. for $C_{59}H_{79}N_9O_{21}S \cdot 6H_2O$:

C 50.96, H 6.60, N 9.07

Found: C 50.89, H 6.43, N 8.98

Example 71

IR (KBr): 3371.0, 1631.5, 1538.9, 1506.1, 1450.2,
1436.7, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.2 (12H, m), 1.2-5.5 (58H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 7.01 (1H,
d, $J=1.7\text{Hz}$), 7.12 (2H, d, $J=8.9\text{Hz}$), 7.45 (1H, d,
 $J=9.2\text{Hz}$), 7.54 (1H, s), 7.5-7.9 (2H, m), 7.85 (2H,
d, $J=8.8\text{Hz}$), 7.99 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d,
 $J=8.9\text{Hz}$), 8.1-8.4 (1H, m), 8.70 (1H, m), 8.86 (1H,
d, $J=7.8\text{Hz}$)

MASS (m/z): 1363.5 ($M^- - 1$)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{88}\text{N}_{10}\text{O}_{21}\text{S} \cdot 7\text{H}_2\text{O}$:

C 51.53, H 6.89, N 9.39

Found: C 51.23, H 6.80, N 9.27

Example 72

IR (KBr): 3363.2, 1666.2, 1648.8, 1538.9, 1506.1,
1454.1, 1436.7, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.2 (12H, m), 1.2-5.3 (60H, m),
6.71 (1H, d, $J=8.2\text{Hz}$), 6.7-6.9 (1H, m), 7.01 (1H,
s), 7.12 (2H, d, $J=8.9\text{Hz}$), 7.54 (1H, s), 7.3-7.8
(3H, m), 7.85 (2H, d, $J=8.7\text{Hz}$), 7.9-8.2 (4H, m),
8.2-8.4 (1H, m), 8.7 (1H, s), 8.8-9.0 (1H, m)

MASS (m/z): 1377.6 ($M^- - 1$)

Elemental Analysis Calcd. for $\text{C}_{65}\text{H}_{90}\text{N}_{10}\text{O}_{21}\text{S} \cdot 8\text{H}_2\text{O}$:

C 51.24, H 7.01, N 9.19

Found: C 51.52, H 7.06, N 9.16

Example 73

IR (KBr): 3363.2, 1631.5, 1538.9, 1510.0, 1438.6,
1243.9 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.11 (3H, d,
 $J=5.7\text{Hz}$), 1.18 (6H, d, $J=6.0\text{Hz}$), 1.2-5.5 (44H, m),
6.71 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=9.8\text{Hz}$), 7.00
(1H, s), 7.11 (2H, d, $J=8.9\text{Hz}$), 7.46 (1H, s), 7.3-

7.8 (3H, m), 7.76 (2H, d, $J=8.7\text{Hz}$), 7.99 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=8.7\text{Hz}$), 8.2-9.0 (3H, m)
MASS (m/z): 1249.4 (M^{-1})

5 Example 74

MASS (m/z): 1377.4 (M^{+1})

Example 75

MASS (m/z): 1405.4 (M^{+1})

10

Example 76

NMR (DMSO- d_6 , δ): 0.86 (3H, d, $J=6.3\text{Hz}$), 0.98 (3H, d, $J=6.8\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.20-5.23 (56H, m), 6.69-8.93 (17H, m)

15

MASS (m/z): 1333.4 (M^{+1})

Example 77

MASS (m/z): 1297.3 (M^{+1})

20 Example 78

A mixture of starting compound (78) (100 mg), N-tert-butoxycarbonyl- β -alanine (13.5 mg), 1-hydroxybenzotriazole (15.5 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (29.4 mg) and N,N-diisopropylethylamine (28.2 μl) in N,N-dimethylformamide (1 ml) was stirred for 3 hours at 30°C. To the reaction mixture was added ethyl acetate (30 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (137.3 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (30% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (78).

35

IR (KBr): 3372.9, 1658.5, 1635.3, 1546.8, 1529.3,
1517.7, 1444.4, 1255.4 cm^{-1}

MASS (m/z): 1468.3 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{66}\text{H}_{90}\text{N}_{11}\text{NaO}_{23}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 49.52, H 6.42, N 9.63

Found: C 49.34, H 6.33, N 9.73

The following compounds [Examples 79 to 86] were
obtained according to a similar manner to that of Example 78.

Example 79

IR (KBr): 3374.8, 1658.5, 1635.3, 1529.3, 1517.7,
1444.4, 1257.4 cm^{-1}

MASS (m/z): 1368.3 (M^- -Na)

Example 80

IR (KBr): 3372.9, 1656.6, 1635.3, 1531.2, 1517.7,
1444.4, 1255.4 cm^{-1}

MASS (m/z): 1496.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{94}\text{N}_{11}\text{NaO}_{23}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 50.15, H 6.56, N 9.46

Found: C 49.90, H 6.36, N 9.34

Example 81

IR (KBr): 3392.2, 1664.3, 1635.3, 1446.4, 1255.4 cm^{-1}

MASS (m/z): 1611.5 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{73}\text{H}_{103}\text{N}_{12}\text{NaO}_{25}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 49.76, H 6.69, N 9.54

Found: C 49.73, H 6.59, N 9.46

Example 82

IR (KBr): 3372.9, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1255.4 cm^{-1}

MASS (m/z): 1498.5 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{67}\text{H}_{92}\text{N}_{11}\text{NaO}_{24}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 48.28, H 6.53, N 9.24

Found: C 48.50, H 6.35, N 9.21

Example 83

5 IR (KBr): 3378.7, 1658.5, 1635.3, 1546.6, 1529.3,
1517.7, 1446.4, 1255.4 cm^{-1}

MASS (m/z): 1625.5 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{74}\text{H}_{105}\text{N}_{12}\text{NaO}_{25}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 49.55, H 6.80, N 9.37

10 Found: C 49.70, H 6.68, N 9.38

Example 84

IR (KBr): 3367.7, 1658.5, 1635.3, 1546.6, 1529.3,
1517.7, 1444.4, 1255.4 cm^{-1}

15 MASS (m/z): 1634.6 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{74}\text{H}_{100}\text{N}_{13}\text{NaO}_{25}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 49.80, H 6.44, N 10.20

Found: C 49.71, H 6.34, N 10.29

20 Example 85

IR (KBr): 3355.5, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1446.4, 1257.4 cm^{-1}

MASS (m/z): 1693.5 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{80}\text{H}_{101}\text{N}_{12}\text{NaO}_{25}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

25 C 52.11, H 6.29, N 9.12

Found: C 51.96, H 6.28, N 9.06

Example 86

30 IR (KBr): 3372.9, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1446.4, 1257.4 cm^{-1}

MASS (m/z): 1645.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{76}\text{H}_{101}\text{N}_{12}\text{NaO}_{25}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 52.32, H 6.50, N 9.27

Found: C 50.56, H 6.37, N 9.29

35

The following compounds [Examples 87 to 95] were obtained according to a similar manner to that of Preparation 10.

5 Example 87

IR (KBr): 2935, 1651, 1541, 1514, 1454, 1514, 1257 cm^{-1}

NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, br s), 1.20-5.00 (44H, m), 3.21 (3H, s), 3.31 (2H, t, $J=6.4\text{Hz}$), 4.07 (2H, t, $J=6.2\text{Hz}$), 6.70-6.80 (2H, m), 7.00 (1H, s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.98 (2H, d, $J=8.9\text{Hz}$), 8.09 (4H, br s)

MASS (m/z): 1443.3 ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{81}\text{N}_{10}\text{O}_{23}\text{S}_2\text{Na} \cdot 7\text{H}_2\text{O}$:

C 48.12, H 6.19, N 9.05

15 Found: C 47.94, H 6.07, N 8.99

Example 88

MASS (m/z): 1492 (M^+)

20 Example 89

IR (KBr): 3490, 3463, 3455, 3423, 3363, 2937, 1631, 1544 cm^{-1}

NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.21 (3H, d, $J=5.4\text{Hz}$), 1.20-1.40 (9H, m), 1.40-2.40 (12H, m), 2.90-3.20 (3H, m), 3.21 (3H, s), 3.33 (3H, t, $J=6.4\text{Hz}$), 3.65-4.30 (9H, m), 4.40-5.00 (6H, m), 5.11-5.30 (6H, m), 5.80-6.10 (1H, m), 6.69-6.80 (2H, m), 6.96 (1H, br s), 7.13 (1H, br s), 7.40-7.90 (3H, m), 8.00-8.30 (7H, m), 8.47 (2H, d, $J=8.3\text{Hz}$), 8.72 (1H, br s), 8.75-8.90 (1H, m)

MASS (m/z)(API-ES-Negative): 1415 ($\text{M}^+ - 1 - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{81}\text{N}_{10}\text{NaO}_{24}\text{S}_2 \cdot 2.5\text{H}_2\text{O}$:

C 50.20, H 5.80, N 9.45

Found: C 50.05, H 5.80, N 9.29

Example 90

IR (KBr): 3369, 1639, 1542, 1519, 1272 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d, $J=5.8\text{Hz}$), 1.20-1.35 (12H, m), 1.35-1.70 (6H, m), 1.70-2.40 (6H, m), 3.17 (3H, s), 3.25 (3H, t, $J=6.3\text{Hz}$), 3.30-3.50 (2H, m), 3.60-4.30 (9H, m), 4.40-4.90 (6H, m), 5.10-5.30 (6H, m), 5.80-5.90 (1H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.60-6.80 (1H, m), 10 6.96 (1H, br s), 7.00-7.20 (1H, m), 7.40-7.90 (3H, m), 8.00-8.20 (6H, m), 8.48 (2H, d, $J=8.4\text{Hz}$), 8.72 (1H, br s), 8.70-8.8 (1H, m)

MASS (m/z): 1441 ($M^+-1-\text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{10}\text{NaO}_{24}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

15 C 48.82, H 6.17, N 8.90
Found: C 48.83, H 6.24, N 8.78

Example 91

IR (KBr): 3363, 2935, 1637, 1626, 1540, 1261 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.30-1.60 (12H, m), 1.70-2.50 (7H, m), 2.80-3.25 (3H, m), 3.21 (3H, s), 3.30 (2H, t, $J=6.5\text{Hz}$), 3.65-4.30 (12H, m), 4.40-5.00 (9H, m), 5.10-5.40 (7H, m), 5.80-6.05 (1H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 25 6.75 (1H, dd, $J=8.3$ and 1.6Hz), 6.96 (1H, d, $J=1.6\text{Hz}$), 7.10 (1H, br s), 7.20 (1H, d, $J=8.8\text{Hz}$), 7.40-7.80 (3H, m), 8.00-8.20 (7H, m), 8.72 (1H, br s), 8.70-8.80 (1H, m)

MASS (m/z) (API-ES-Negative): 1367 ($M^++1-\text{Na}$)

30 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{81}\text{N}_{10}\text{NaO}_{23}\text{S} \cdot 6\text{H}_2\text{O}$:

C 69.70, H 6.21, N 9.35
Found: C 49.86, H 6.22, N 9.35

Example 92

35 IR (KBr): 3363, 2933, 2859, 1637, 1540, 1510, 1444,

1261 cm^{-1}

5 NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.28-1.60 (15H, m), 1.69-2.45 (8H, m),
2.80-3.30 (3H, m), 3.20 (3H, s), 3.26 (2H, t, $J=6.4\text{Hz}$), 3.60-4.30 (12H, m), 4.40-5.00 (9H, m),
5.10-5.30 (7H, m), 5.75-6.05 (1H, m), 6.68 (1H, d, $J=8.1\text{Hz}$), 6.75 (1H, dd, $J=1.7$ and 8.3Hz), 6.96 (1H, d, $J=1.7\text{Hz}$), 7.10-7.20 (1H, m), 7.15 (2H, d, $J=8.9\text{Hz}$), 7.40-7.90 (3H, m), 8.00-8.20 (7H, m),
10 8.60-8.80 (2H, m)

MASS (m/z) (APCI-ES-Negative): 1395 ($M^+ + 1 - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{10}\text{NaO}_{23}\text{S} \cdot 6\text{H}_2\text{O}$:

C 50.36, H 6.36, N 9.18

Found: C 50.22, H 6.31, N 9.10

15

Example 93

MASS (m/z): 1461.4 ($M^+ - 1$)

Example 94

20 MASS (m/z): 1489.5 ($M^+ - 1$)

Example 95

25 NMR (DMSO-d_6 , δ): 0.87 (3H, d, $J=6.3\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14-5.29 (81H, m), 6.69-8.72 (18H, m)
MASS (m/z): 1418.4 (free)

The following compounds [Examples 96 to 117] were obtained according to a similar manner to that of Example 19.

30 Example 96

IR (KBr): 1632, 1539, 1520, 1443 cm^{-1}

35 NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.97 (3H, d, $J=6.64\text{Hz}$), 1.07 (3H, d, $J=5.68\text{Hz}$), 1.15-1.70 (3H, m), 1.70-2.50 (5H, m), 2.70-3.40 (5H, m), 4.10-4.60 (8H, m), 4.70-4.85 (2H, m), 5.00-5.35 (2H, m), 5.70-6.10

(1H, m), 6.50-6.80 (2H, m), 6.99 (1H, s)

ESI MASS (m/z)(Positive): 1019.3 ($M^+ + Na$)

Elemental Analysis Calcd. for $C_{39}H_{57}N_8O_{19}SNa \cdot 8H_2O$:

C 41.05, H 6.45, N 9.82

5

Found: C 41.02, H 6.19, N 9.73

Example 97

IR (KBr): 1647, 1635, 1539, 1518, 1439, 1269 cm^{-1}

10 NMR (DMSO- d_6 + D_2O , δ): 0.95 (3H, d, $J=6.66Hz$), 1.12
(3H, d, $J=5.76Hz$), 1.20-1.60 (4H, m), 1.70-2.45
(4H, m), 2.65-3.35 (6H, m), 3.70-4.55 (16H, m),
4.60-4.80 (2H, m), 5.10-5.40 (2H, m), 5.70-6.00
(1H, m), 6.75 (1H, d, $J=8.15Hz$), 6.83 (1H, d,
 $J=10.1Hz$), 7.09 (1H, s)

15

ESI MASS (m/z)(Negative): 989.3 (M^+)

Elemental Analysis Calcd. for $C_{39}H_{58}N_8O_{20}SNa \cdot 5H_2O$:

C 43.33, H 6.34, N 10.37

Found: C 43.17, H 6.25, N 10.30

20 Example 98

IR (KBr): 1680, 1662, 1639, 1539, 1514, 1439 cm^{-1}

25 NMR (DMSO- d_6 + D_2O , δ): 0.98 (3H, d, $J=6.77Hz$), 1.09
(3H, d, $J=6.01Hz$), 1.15-1.40 (1H, m), 1.45-2.00
(4H, m), 2.10-2.50 (4H, m), 2.70-2.90 (3H, m),
3.15-3.40 (4H, m), 3.70-4.00 (6H, m), 4.10-4.50
(6H, m), 4.75-4.80 (2H, m), 6.70-6.80 (2H, m), 7.03
(1H, s)

ESI MASS (m/z)(Positive): 892.2 ($M^+ + 1$)

Elemental Analysis Calcd. for $C_{35}H_{54}N_8O_{17}S \cdot 4H_2O$:

30

C 43.65, H 6.49, N 11.64

Found: C 43.51, H 6.40, N 11.48

Example 99

NMR (DMSO- d_6 + D_2O , δ): 0.96 (3H, d, $J=6.69Hz$), 1.09

(3H, d, $J=5.05\text{Hz}$), 1.15-2.40 (8H, m), 2.65-3.30
(3H, m), 3.70-4.90 (18H, m), 6.65-6.85 (2H, m),
6.99 (1H, s)

ESI MASS (m/z)(Positive): 1013.4 ($M^+ + \text{Na}$)

5

Example 100

IR (KBr): 3377, 2935, 1658.5, 1641, 1531, 1518, 1444,
1284, 1257, 1113, 1088, 1043 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.05 (3H, d,
 $J=5.6\text{Hz}$), 3.21 (3H, s), 4.07 (2H, t, $J=6.5\text{Hz}$), 1.2-
5.2 (57H, complex m), 6.70 (1H, d, $J=8.1\text{Hz}$), 6.78-
6.83 (1H, m), 6.99 (1H, br s), 7.13 (2H, d,
15 $J=8.8\text{Hz}$), 7.4-7.6 (2H, m), 7.7-7.9 (1H, m), 7.97
(2H, d, $J=8.8\text{Hz}$), 8.09 (4H, s), 8.50-8.60 (1H, m),
8.71 (1H, s), 8.68-8.80 (1H, m)

MASS (m/z): 1407.3 (M^+)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{11}\text{O}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 50.09, H 6.50, N 10.04

Found: C 50.01, H 6.41, N 9.91

20

Example 101

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.1-5.6 (72H,
m), 6.6-6.9 (2H, m), 6.99 (1H, s), 7.14 (2H, d,
 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (4H, s), 7.4-
25 9.0 (6H, m)

MASS (m/z): 1411.3 ($M^- - 1$)

Example 102

IR (KBr): 3384.5, 1658.5, 1635.3, 1444.4, 1257.4 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d,
 $J=5.3\text{Hz}$), 1.3-5.4 (62H, m), 6.70 (1H, d, $J=8.2\text{Hz}$),
6.77 (1H, d, $J=9.8\text{Hz}$), 6.96 (1H, s), 7.13 (2H, d,
 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d,
 $J=8.8\text{Hz}$), 8.11 (2H, d, $J=8.9\text{Hz}$), 7.4-9.0 (6H, m)

MASS (m/z): 1354.3 (M^{-1})

Example 103

5 IR (KBr): 3401.8, 1664.3, 1635.3, 1627.6, 1446.4,
1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.0-5.6 (69H, m), 6.68 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=8.7\text{Hz}$), 6.93 (1H, d, $J=8.4\text{Hz}$), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.08 (4H, s), 7.4-9.0 (6H, m)

10 MASS (m/z): 1382.4 (M^{-1})

Example 104

15 IR (KBr): 3403.7, 1664.3, 1635.3, 1446.4, 1257.4 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.0-5.5 (71H, m), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 6.6-8.9 (13H, m)

MASS (m/z): 1420.2 ($M^{+}+\text{Na}$)

Example 105

20 IR (KBr): 3367.1, 1635.3, 1531.2, 1517.7, 1444.4,
1257.4 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.12 (3H, d, $J=5.9\text{Hz}$), 1.2-5.4 (64H, m), 6.70 (1H, d, $J=8.1\text{Hz}$), 6.77 (1H, d, $J=10.0\text{Hz}$), 6.99 (1H, s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.44 (1H, d, $J=8.6\text{Hz}$), 7.62 (1H, m), 7.78 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d, $J=8.8\text{Hz}$), 8.11 (2H, d, $J=8.7\text{Hz}$), 8.1-8.3 (1H, m), 8.6-8.9 (2H, m)

MASS (m/z): 1368.5 (M^{-1})

30 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{87}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 49.16, H 6.85, N 10.17

Found: C 49.29, H 6.50, N 10.08

Example 106

IR (KBr): 2935.1, 2865.7, 1648.8, 1538.9, 1513.8,
1452.1, 1440.6, 1257.4 cm^{-1}

5 NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.3\text{Hz}$), 1.11 (3H,
d, $J=5.7\text{Hz}$), 1.2-4.9 (55H, complex m), 3.21 (3H,
s), 3.31 (2H, t, $J=6.5\text{Hz}$), 6.7-6.81 (2H, m), 7.03
(1H, br s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.98 (2H, d,
 $J=8.9\text{Hz}$), 8.0-8.15 (4H, m)

MASS (m/z): 1463.4 (M^+-1)

10 Elemental Analysis Calcd. for $\text{C}_{67}\text{H}_{92}\text{N}_{12}\text{O}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 50.56, H 6.71, N 10.56

Found: C 50.34, H 6.38, N 10.46

Example 107

15 IR (KBr): 2933, 2860, 1657, 1635, 1529, 1516, 1444,
1387, 1257, 1178, 1115, 1088, 1043 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H,
d, $J=5.9\text{Hz}$), 1.4-4.85 (50H, complex m), 3.21 (3H,
s), 3.31 (2H, t, $J=6.3\text{Hz}$), 6.7-6.8 (2H, m), 7.02
20 (1H, br s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d,
 $J=8.9\text{Hz}$), 8.02-8.14 (4H, m)

MASS (m/z): 1381.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{87}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 50.76, H 6.69, N 10.34

25 Found: C 50.43, H 6.70, N 10.20

Example 108

IR (KBr): 2935, 2866, 1660, 1631.5, 1525, 1442.5, 1412,
1257, 1178, 1111, 1088, 1043 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.5\text{Hz}$), 1.2-4.9 (55H, complex m), 3.21 (3H, s),
3.31 (2H, t, $J=6.4\text{Hz}$), 6.75 (2H, br), 7.05 (1H,
br), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.99 (2H, d, $J=8.8\text{Hz}$),
8.01-8.16 (4H, m)

MASS (m/z): 1510.5 (M^+-1)

Elemental Analysis Calcd. for $C_{68}H_{94}N_{12}O_{23}S_2 \cdot 7H_2O$:

C 49.87, H 6.65, N 10.26

Found: C 49.64, H 6.57, N 10.15

5

Example 109

IR (KBr): 3372.9, 1658.5, 1635.3, 1529.3, 1517.7,
1446.4, 1255.4 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7Hz$), 1.15 (3H, d,
 $J=5.1Hz$), 1.2-5.6 (58H, m), 6.71 (1H, d, $J=8.1Hz$),
6.77 (1H, d, $J=10.0Hz$), 6.97 (1H, s), 7.13 (2H, d,
 $J=8.9Hz$), 7.97 (2H, d, $J=8.8Hz$), 8.09 (4H, s), 7.3-
9.0 (7H, m)

MASS (m/z): 1510.5 (M^-Na)

15 Elemental Analysis Calcd. for $C_{61}H_{82}N_{11}NaO_{21}S_2 \cdot 8H_2O$:

C 47.68, H 6.43, N 10.03

Found: C 49.75, H 6.19, N 10.23

Example 110

20 IR (KBr): 3374.8, 1658.5, 1635.3, 1529.3, 1517.7,
1444.4, 1257.4 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8Hz$), 1.13 (3H, d,
 $J=5.6Hz$), 1.2-5.4 (64H, m), 6.71 (1H, d, $J=8.1Hz$),
6.78 (1H, d, $J=10.0Hz$), 7.03 (1H, s), 7.13 (2H, d,
 $J=8.9Hz$), 7.97 (2H, d, $J=8.7Hz$), 8.0-8.2 (4H, m),
7.3-9.0 (7H, m)

MASS (m/z): 1410.54 (M^-Na)

30 Elemental Analysis Calcd. for $C_{64}H_{88}N_{11}NaO_{21}S_2 \cdot 6H_2O$:

C 49.83, H 6.53, N 9.99

Found: C 49.72, H 6.40, N 9.99

Example 111

IR (KBr): 3374.8, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1257.4 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d,
 $J=5.4\text{Hz}$), 1.2-5.6 (62H, m), 6.71 (1H, d, $J=8.2\text{Hz}$),
6.78 (1H, d, $J=9.8\text{Hz}$), 7.02 (1H, s), 7.13 (2H, d,
 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.06 (2H, d,
 $J=9.1\text{Hz}$), 8.11 (2H, d, $J=8.8\text{Hz}$), 7.3-9.0 (7H, m)

MASS (m/z): 1396.4 (M^- -Na)

10 Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{11}\text{NaO}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:
C 48.92, H 6.52, N 9.96
Found: C 48.92, H 6.32, N 9.85

Example 112

15 IR (KBr): 3359.4, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d,
 $J=5.8\text{Hz}$), 1.2-5.8 (64H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.77 (1H, d, $J=9.7\text{Hz}$), 6.98 (1H, s), 7.13 (2H, d,
20 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (4H, s), 7.3-
9.0 (7H, m)

MASS (m/z): 1411.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{85}\text{N}_{12}\text{NaO}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:
C 48.45, H 6.52, N 10.76
25 Found: C 48.44, H 6.32, N 10.62

Example 113

IR (KBr): 3374.8, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1257.4 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.5\text{Hz}$), 1.11 (3H, d,
 $J=4.5\text{Hz}$), 1.2-5.8 (60H, m), 6.68 (1H, d, $J=8.0\text{Hz}$),
6.80 (1H, d, $J=7.9\text{Hz}$), 6.93 (1H, d, $J=9.5\text{Hz}$), 7.13
(2H, d, $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (4H,
s), 7.3-9.0 (7H, m)

MASS (m/z): 1398.4 (M^- -Na)

Example 114

IR (KBr): 3374.8, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.5\text{Hz}$), 1.15 (3H, d,
 $J=5.8\text{Hz}$), 1.2-5.6 (65H, m), 6.70 (1H, d, $J=8.2\text{Hz}$),
6.77 (1H, d, $J=9.8\text{Hz}$), 6.97 (1H, s), 7.13 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (4H, s), 7.3-
9.0 (7H, m)

MASS (m/z): 1398.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{89}\text{N}_{12}\text{NaO}_{21}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 47.69, H 6.69, N 10.43

Found: C 47.78, H 6.32, N 10.17

Example 115

MASS (m/z): 1434.4 (M^- -Na)

Example 116

IR (KBr): 3348, 1658.5, 1633 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.82-0.89 (3H, m), 0.95-1.03
(6H, m), 1.1-4.78 (57H, complex m), 6.7-6.8 (2H,
m), 7.03 (1H, br s)

MASS (m/z): 1128.5 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{51}\text{H}_{84}\text{N}_8\text{O}_{18}\text{S} \cdot 5\text{H}_2\text{O}$:

C 50.23, H 7.77, N 9.19

Found: C 50.10, H 7.78, N 9.09

Example 117

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.6\text{Hz}$), 1.10 (3H, d,
 $J=5.4\text{Hz}$), 0.74-2.69 (22H, m), 2.80-3.05 (3H, m),
3.15-4.62 (18H, m), 4.68-5.35 (8H, m), 6.71 (1H, d,
 $J=8.1\text{Hz}$), 6.78 (1H, d, $J=8.1\text{Hz}$), 7.01 (1H, s), 7.12
(2H, d, $J=8.6\text{Hz}$), 7.37-8.10 (3H, m), 7.73 (4H, d,
 $J=8.5\text{Hz}$), 7.97 (2H, d, $J=8.3\text{Hz}$), 8.22-8.40 (1H, m),

8.65-8.88 (2H, m)

MASS (m/z): 1224.4 (M^+-1)

Example 118

5 To a solution of a mixture of starting compound (118)
(440 mg), 1-1-dimethyl-4-oxo-piperidinium Iodide(122 mg) and
acetic acid (55 μ l) in a mixture of methanol (6 ml) and DMF
(3 ml) was added sodium cyanoborohydride (30 mg) with
10 stirring at ambient temperature, and the mixture was stirred
at the same temperature overnight. To the reaction mixture
was added ethyl acetate and the resulting precipitates were
collected by filtration and dried in vacuo. The precipitates
were dissolved in a mixture of pH 6.86 standard buffer
15 solution and acetonitrile, and the solution was subjected to
column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B
(Trademark: prepared by Daiso Co., Ltd.)) eluting with 30%
acetonitrile in water. The fractions containing the object
compound were collected and evaporated under reduced pressure
to remove acetonitrile. The residue was lyophilized to give
20 object compound (118) (350 mg).

IR (KBr): 3353, 2942, 1673, 1633, 1517, 1463, 1438,
1268, 1232, 1201, 1135, 1085, 1045 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.3-1.6 (6H, m), 1.6-2.7 (17H, m), 2.7-
25 4.2 (37H, m), 4.2-4.6 (7H, m), 4.80 (2H, d,
 $J=6.7\text{Hz}$), 5.2 (1H, m), 5.4 (1H, m), 6.77 (2H, m),
7.05 (1H, s), 7.08 (2H, d, $J=8.3\text{Hz}$), 7.45 (1H, d,
 $J=8.8\text{Hz}$), 7.56 (1H, d, $J=7.5\text{Hz}$), 7.75 (2H, d,
 $J=8.8\text{Hz}$), 7.90 (1H, m), 7.96 (4H, s), 8.40 (1H, d,
30 $J=7.2\text{Hz}$), 8.6 (1H, m), 8.70 (1H, d, $J=6.9\text{Hz}$), 8.79
(1H, s)

MASS (m/z): 1513.3 ($M^++\text{Na}$)

The following compounds [Examples 119 to 137] were
35 obtained according to a similar manner to that of Example

118.

Example 119

IR (KBr): 3353, 2937, 1673, 1635, 1529, 1517, 1463,
5 1436, 1230, 1199, 1133, 1085, 1045 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.30 (4H, m), 1.50 (6H, m), 1.6-2.7 (17H,
m), 2.7-4.2 (37H, m), 4.2-4.6 (7H, m), 4.80 (2H, d,
 $J=6.7\text{Hz}$), 5.14 (1H, m), 5.35 (1H, m), 6.72 (1H, d,
10 $J=8.8\text{Hz}$), 6.80 (1H, d, $J=8.8\text{Hz}$), 7.05 (1H, s), 7.08
(2H, d, $J=8.8\text{Hz}$), 7.45 (1H, d, $J=8.8\text{Hz}$), 7.56 (1H,
d, $J=7.5\text{Hz}$), 7.75 (2H, d, $J=8.8\text{Hz}$), 7.91 (1H, m),
7.96 (4H, s), 8.40 (1H, d, $J=7.2\text{Hz}$), 8.6 (1H, m),
8.70 (1H, d, $J=6.9\text{Hz}$), 8.80 (1H, s)

15 MASS (m/z): 1541.6 (M^+ +Na)

Elemental Analysis Calcd. for $\text{C}_{71}\text{H}_{99}\text{N}_{13}\text{O}_{20}\text{S}_2 \cdot 2\text{TFA} \cdot 9\text{H}_2\text{O}$:

C 47.19, H 6.28, N 9.54

Found: C 47.13, H 6.01, N 9.47

20 Example 120

IR (KBr): 3355, 2937, 1673, 1635, 1529, 1519, 1444,
1276, 1253, 1201, 1135, 1085, 1045 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 0.98 (3H, d,
 $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.56 (5H, m), 1.6-
25 2.7 (17H, m), 2.8-3.8 (26H, m), 3.8-4.2 (9H, m),
4.2-4.6 (7H, m), 4.8 (3H, m), 5.17 (1H, m), 5.4
(1H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.80 (1H, d,
 $J=8.2\text{Hz}$), 7.05 (1H, s), 7.20 (2H, d, $J=8.8\text{Hz}$), 7.44
(1H, d, $J=7.8\text{Hz}$), 7.62 (1H, d, $J=7.8\text{Hz}$), 7.8 (1H,
30 m), 7.93 (2H, d, $J=8.8\text{Hz}$), 8.07 (2H, d, $J=8.8\text{Hz}$),
8.11 (2H, d, $J=8.8\text{Hz}$), 8.30 (1H, d, $J=7.8\text{Hz}$), 8.67
(1H, m), 8.85 (1H, d, $J=7.8\text{Hz}$)

MASS (m/z): 1465.9 (M^+ +Na)

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{95}\text{N}_{13}\text{O}_{18}\text{S}_2 \cdot 4\text{TFA} \cdot 8\text{H}_2\text{O}$:

C 44.60, H 5.66, N 8.90

Found: C 44.70, H 5.59, N 8.95

Example 121

5 IR (KBr): 3355.5, 1635.3, 1533.1, 1515.8, 1417.4,
1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.14 (3H, d,
 $J=5.4\text{Hz}$), 1.2-5.6 (68H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.78 (1H, d, $J=9.5\text{Hz}$), 7.02 (1H, s), 7.14 (2H, d,
10 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.05 (2H, d,
 $J=8.6\text{Hz}$), 8.10 (2H, d, $J=8.5\text{Hz}$), 7.4-9.0 (6H, m)

MASS (m/z): 1432.4 ($M^+ + \text{Na}$)Elemental Analysis Calcd. for $\text{C}_{65}\text{H}_{91}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 50.80, H 6.89, N 10.03

15 Found: C 50.59, H 6.84, N 10.00

Example 122

IR (KBr): 3374.8, 1648.8, 1631.5, 1538.9, 1513.8,
1450.2, 1442.5, 1257.4 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8\text{Hz}$), 1.0-5.4 (65H,
m), 6.6-6.9 (2H, m), 7.00 (1H, s), 7.14 (2H, d,
 $J=8.4\text{Hz}$), 7.97 (2H, d, $J=8.2\text{Hz}$), 8.05 (2H, d,
 $J=8.7\text{Hz}$), 8.11 (2H, d, $J=8.2\text{Hz}$), 7.3-9.0 (7H, m)

MASS (m/z): 1429.3 ($M^- - 1$)

25 Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{10}\text{O}_{22}\text{S}_3 \cdot 5\text{H}_2\text{O}$:

C 49.73, H 6.36, N 9.20

Found: C 49.56, H 6.74, N 9.18

Example 123

30 IR (KBr): 2935, 2864, 1649, 1539, 1514, 1450, 1442.5,
1257 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H,
d, $J=5.7\text{Hz}$), 1.2-4.9 (46H, complex m), 3.21 (3H,
s), 3.31 (2H, t, $J=6.4\text{Hz}$), 5.63 (1H, s), 6.7-6.8
35 (2H, m), 7.02 (1H, br s), 7.15 (2H, d, $J=8.8\text{Hz}$),

7.32 (5H, s), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.06 (4H, s)
MASS (m/z): 1460.4 (M^+)

Elemental Analysis Calcd. for $C_{68}H_{88}N_{10}O_{22}S_2 \cdot 6H_2O$:

C 52.03, H 6.42, N 8.92

5

Found: C 51.77, H 6.39, N 8.77

Example 124

IR (KBr): 2935, 1664.3, 1631.5, 1606.4, 1442.5,
1411.6 cm^{-1}

10

NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H,
d, $J=5.4\text{Hz}$), 1.33 (6H, d, $J=6.3\text{Hz}$), 1.32-4.81 (46H,
complex m), 3.21 (3H, s), 3.31 (2H, t, $J=6.5\text{Hz}$),
6.7-6.8 (2H, m), 7.03 (1H, br s), 7.14 (2H, d,
 $J=8.8\text{Hz}$), 7.98 (2H, d, $J=8.8\text{Hz}$), 8.08 (4H, s)

15

MASS (m/z): 1411.5 (M^+-1)

Elemental Analysis Calcd. for $C_{64}H_{88}N_{10}O_{22}S_2 \cdot 5H_2O$:

C 51.12, H 6.57, N 9.32

Found: C 51.37, H 6.49, N 9.34

20 Example 125

IR (KBr): 3355, 2937, 1673, 1631, 1535, 1515, 1442,
1259, 1201, 1180, 1133, 1087, 1045 cm^{-1}

25

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.3-1.6 (9H, m), 1.6-2.7 (17H, m), 3.21
(3H, s), 2.8-3.6 (12H, m), 3.6-4.2 (14H, m), 4.2-
4.6 (7H, m), 4.83 (3H, m), 5.0 (1H, m), 5.15 (2H,
m), 5.30 (2H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H,
d, $J=8.2\text{Hz}$), 7.05 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$),
7.46 (1H, d, $J=8.4\text{Hz}$), 7.57 (1H, d, $J=8.4\text{Hz}$), 7.88
(1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d,
 $J=8.5\text{Hz}$), 8.12 (2H, d, $J=8.5\text{Hz}$), 8.42 (1H, m), 8.7
(1H, m), 8.93 (1H, d, $J=8.4\text{Hz}$)

30

MASS (m/z): 1408.94 (M^+-Na)

Elemental Analysis Calcd. for $C_{66}H_{93}N_{11}O_{21}S_2 \cdot 2TFA \cdot 5H_2O$:

Calcd: C 47.80, H 6.02, N 8.76
Found: C 47.80, H 6.27, N 8.90

Example 126

5 **MASS (m/z):** 1612.5 (M⁻-1)+1

Example 127

IR (KBr): 3353.6, 1664.3, 1627.6, 1446.4, 1257.4 cm^{-1}

MASS (m/z): 1454.4 (M⁻-1)

10 Elemental Analysis Calcd. for $C_{86}H_{93}N_{11}O_{22}S_2 \cdot 7H_2O$:

C 50.09, H 6.81, N 9.73

Found: C 49.80, H 6.81, N 9.73

Example 128

15 IR (KBr): 3353.6, 1658.5, 1635.3, 1517.7, 1444.4,
1255.4 cm^{-1}

MASS (m/z): 1482.4 (M⁻-1)

Elemental Analysis Calcd. for $C_{68}H_{97}N_{11}O_{22}S_2 \cdot 6H_2O$:

C 51.28, H 6.90, N 9.67

20 Found: C 51.57, H 6.80, N 9.68

Example 129

IR (KBr): 3401.8, 1664.3, 1635.3, 1446.4, 1255.4 cm^{-1}

MASS (m/z): 1496.5 (M⁻-1)

25

Example 130

major product

IR (KBr): 3351.7, 1658.5, 1635.3, 1517.7, 1444.4,
1255.4 cm^{-1}

30 MASS (m/z): 1469.5 (M⁻-1)+1

Elemental Analysis Calcd. for $C_{67}H_{95}N_{11}O_{22}S_2 \cdot 8H_2O$:

C 49.84, H 6.93, N 9.54

Found: C 49.95, H 6.52, N 9.37

35 minor product

IR (KBr): 3351.7, 1664.3, 1635.3, 1529.3, 1517.7,
1446.4, 1255.4 cm^{-1}
MASS (m/z): 1439.5 (M^{-1})

5 Example 131

IR (KBr): 2935, 1649, 1539, 1514, 1452, 1257 cm^{-1}
MASS (m/z): 1563.4 (M^{+1})
Elemental Analysis Calcd. for $\text{C}_{12}\text{H}_{100}\text{N}_{12}\text{O}_{23}\text{S}_2 \cdot 8\text{H}_2\text{O}$:
C 50.58, H 6.84, N 9.83
10 Found: C 50.43, H 6.69, N 9.81

Example 132

MASS (m/z): 1480.4 (M^{+1})

15 Example 133

The object compound (133) was used directly in the next reaction without purification.

Example 134

20 The object compound (134) was used directly in the next reaction without purification.

Example 135

25 The object compound (135) was used directly in the next reaction without purification.

Example 136

IR (KBr): 1659, 1635, 1444, 1257 cm^{-1}
NMR (DMSO-d_6 , δ): 0.9-1.25 (6H, m), 1.25-2.6 (23H, m),
30 2.6-5.2 (34H, m), 6.65-6.8 (2H, m), 6.98 (2H, m),
7.13 (2H, d, $J=9.0\text{Hz}$), 7.2-7.8 (3H, m), 7.97 (2H,
d, $J=8.8\text{Hz}$), 7.95-8.2 (5H, m), 8.4-8.8 (2H, m)
MASS (m/z): 1363 (M^{+23})
Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{80}\text{N}_{12}\text{O}_{20}\text{S}_2 \cdot 11\text{H}_2\text{O}$:

C 46.03, H 6.68, N 10.92

Found: C 45.83, H 6.26, N 10.72

Example 137

- 5 IR (KBr): 1664, 1605, 1446, 1257 cm^{-1}
NMR (DMSO- d_6 , δ): 0.8-1.2 (6H, s), 1.2-2.7 (23H, m),
2.7-5.4 (38H, m), 6.6-7.0 (2H, m), 7.14 (2H, d,
J=8.8Hz), 7.29 (1H, s), 7.51 (1H, s), 7.4-7.9 (3H,
m), 7.97 (2H, d, J=8.8Hz), 8.0-8.3 (5H, m), 8.6-9.0
10 (2H, m)
MASS (m/z): 1391 (M^+-1)

The following compounds [Examples 138 to 192] were
obtained according to a similar manner to that of Example 1.

15

Example 138

- IR (KBr): 1666, 1632, 1535, 1514, 1441, 1271 cm^{-1}
NMR (DMSO- d_6 + D_2O , δ): 0.98 (3H, d, J=6.72Hz), 1.08
(3H, d, J=5.78Hz), 1.35 (9H, s), 1.45-2.00 (6H, m),
20 2.10-2.40 (3H, m), 2.75-2.95 (3H, m), 3.10-3.40
(2H, m), 3.60-4.50 (14H, m), 4.70-4.80 (2H, m),
6.72 (1H, d, J=8.12Hz), 6.77 (1H, d, J=9.72Hz),
7.02 (1H, s)
ESI MASS (m/z)(Positive): 992 (M^++1)
25 Elemental Analysis Calcd. for $\text{C}_{40}\text{H}_{74}\text{N}_8\text{O}_{25}\text{S}\cdot 6\text{H}_2\text{O}$:
C 43.71, H 6.79, N 10.19
Found: C 43.75, H 6.71, N 10.11

Example 139

- 30 IR (KBr): 3324, 2975, 2937, 1631, 1610, 1529, 1519,
1465, 1446, 1240, 1176, 1085, 1045 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=5.7Hz), 1.18 (6H, d, J=6.2Hz), 1.6-2.1 (3H, m),
2.1-2.6 (6H, m), 2.98 (2H, m), 3.20 (1H, m), 3.4
35 (2H, m), 3.73 (4H, m), 3.8-4.6 (14H, m), 4.6-5.6

(9H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.81 (1H, d, $J=8.2\text{Hz}$), 6.89 (1H, s), 7.04 (1H, s), 7.11 (2H, d, $J=8.9\text{Hz}$), 7.2-7.7 (4H, m), 7.78 (2H, d, $J=8.9\text{Hz}$), 7.95 (4H, s), 8.07 (1H, m), 8.54 (1H, m), 8.80 (1H, s), 8.95 (1H, s)

MASS (m/z): 1321.2 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{74}\text{N}_{12}\text{O}_{20}\text{S}_2 \cdot 10\text{H}_2\text{O}$:

C 46.33, H 6.30, N 11.18

Found: C 46.26, H 5.98, N 11.04

10

Example 140

IR (KBr): 3355, 2937, 1633, 1629, 1529, 1517, 1467, 1446, 1253, 1176, 1114, 1083, 1045 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.96 (2H, d, $J=6.7\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.2-1.6 (8H, m), 1.6-2.1 (9H, m), 2.1-2.6 (2H, m), 3.0 (3H, m), 3.40 (2H, m), 3.75 (2H, m), 3.9-4.2 (6H, m), 4.2-4.6 (7H, m), 4.6-4.9 (3H, m), 5.0 (1H, m), 5.2 (2H, m), 5.30 (1H, d, $J=4.4\text{Hz}$), 6.69 (1H, d, $J=9.8\text{Hz}$), 6.78 (1H, d, $J=9.8\text{Hz}$), 7.08 (1H, s), 7.15 (2H, d, $J=9.0\text{Hz}$), 7.41 (1H, d, $J=8.8\text{Hz}$), 7.5 (1H, m), 7.77 (1H, m), 7.88 (2H, d, $J=8.8\text{Hz}$), 7.96 (4H, s), 8.34 (1H, d, $J=6.3\text{Hz}$), 8.75 (1H, d, $J=8.5\text{Hz}$), 8.85 (1H, m), 8.86 (1H, s)

25

MASS (m/z): 1306.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{73}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 47.37, H 6.24, N 10.48

Found: C 47.32, H 6.05, N 10.32

30 Example 141

IR (KBr): 3328, 2937, 1635, 1529, 1519, 1465, 1444, 1255, 1178, 1112, 1085, 1045 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.2 (2H, m), 1.4-2.1 (14H, m), 2.2-2.5 (3H, m), 2.90 (3H, m), 3.22 (3H, s), 3.75 (2H, m),

35

3.8-4.2 (9H, m), 4.2-4.6 (6H, m), 4.8 (3H, m), 5.2
(2H, m), 5.3 (1H, m), 6.70 (1H, d, J=8.2Hz), 6.80
(1H, d, J=8.2Hz), 7.08 (1H, s), 7.15 (2H, d,
J=8.8Hz), 7.42 (1H, d, J=8.0Hz), 7.5 (2H, m), 7.77
(1H, m), 7.90 (2H, d, J=8.8Hz), 7.96 (4H, s), 8.3
(1H, m), 8.73 (1H, d, J=6.5Hz), 8.86 (1H, s)

MASS (m/z): 1324.3 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{75}N_{11}O_{21}S_2 \cdot 9H_2O$:

C 46.80, H 6.30, N 10.35

Found: C 46.66, H 6.13, N 10.12

Example 142

IR (KBr): 1651, 1539, 1514, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 0.85-1.3 (12H, m), 1.5-2.6 (10H, m),
2.7-3.6 (18H, m), 3.6-5.4 (24H, m), 6.65-7.2 (9H,
m), 7.3-8.0 (9H, m), 8.2-8.45 (1H, m), 8.6-8.95
(2H, m)

MASS (m/z): 1358 (M^+-1)

Elemental Analysis Calcd. for $C_{64}H_{85}N_{11}O_{20}S \cdot 7H_2O$:

C 51.73, H 6.71, N 10.36

Found: C 51.50, H 6.70, N 11.31

Example 143

IR (KBr): 2931, 1659, 1633, 1531, 1506, 1444, 1385 cm^{-1}

NMR (DMSO- d_6 , δ): 0.83 (3H, t, J=6.7Hz), 0.96 (3H, d,
J=6.8Hz), 1.07 (3H, d, J=5.4Hz), 1.18-1.52 (10H,
m), 1.60-2.08 (7H, m), 2.08-2.43 (2H, m), 2.79-3.03
(3H, m), 3.14-3.55 (2H, m), 3.65-4.54 (16H, m),
4.65-5.20 (9H, m), 6.74 (1H, d, J=8.2Hz), 6.83 (1H,
d, J=8.5Hz), 6.97 (2H, d, J=8.8Hz), 7.08 (1H, s),
7.40 (1H, d, J=9.2Hz), 7.33-7.86 (2H, m), 7.85 (2H,
d, J=8.8Hz), 8.31 (1H, d, J=6.6Hz), 8.58 (1H, d,
J=7.8Hz), 8.85 (1H, br s)

MASS (m/z): 1137.4 (M^+-1)

Elemental Analysis Calcd. for $C_{50}H_{74}N_8O_{20}S \cdot 7H_2O$:

C 47.46, H 7.01, N 8.86

Found: C 47.31, H 6.85, N 8.78

Example 144

5 IR (KBr): 3344.0, 1672.0, 1658.5, 1664.3, 1635.3,
1446.4, 1257.4 cm^{-1}
ESI MASS (m/z): 1219 ($\text{M}^+ + 1$)

Example 145

10 IR (KBr): 2974, 2937, 1633, 1537, 1514, 1443, 1269 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.13 (3H, d,
 $J=5.6\text{Hz}$), 1.18 (3H, t, $J=7.0\text{Hz}$), 1.35-2.56 (5H, m),
2.56-2.84 (4H, m), 2.84-3.40 (5H, m), 3.52 (2H, q,
 $J=7.0\text{Hz}$), 3.68-4.60 (13H, m), 4.53 (2H, s), 4.60-
15 5.30 (8H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d,
 $J=8.2\text{Hz}$), 6.96 (1H, s), 7.46 (2H, d, $J=8.3\text{Hz}$), 7.77
(2H, d, $J=8.2\text{Hz}$), 7.58-7.84 (2H, m), 7.92 (2H, d,
 $J=8.5\text{Hz}$), 7.84-8.27 (8H, m), 8.70-8.85 (2H, m)
MASS (m/z): 1287.3 ($\text{M}^+ - 1$)
20 Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{72}\text{N}_{10}\text{O}_{19}\text{S}_2 \cdot 9\text{H}_2\text{O}$:
C 48.82, H 6.25, N 9.65
Found: C 48.73, H 6.01, N 9.45

Example 146

25 IR (KBr): 2939, 1633, 1606, 1535, 1525, 1444, 1419,
1358 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d,
 $J=5.6\text{Hz}$), 1.33-2.78 (16H, m), 2.78-5.00 (26H, m),
4.56 (2H, s), 5.00-5.35 (2H, m), 6.70 (1H, d,
30 $J=8.1\text{Hz}$), 6.77 (1H, d, $J=8.1\text{Hz}$), 6.96 (1H, s), 7.10
(2H, d, $J=9.0\text{Hz}$), 7.20-7.80 (8H, m), 7.84 (2H, d,
 $J=8.8\text{Hz}$), 8.06 (4H, s), 8.00-8.30 (1H, m), 8.40-
8.80 (2H, m)
MASS (m/z): 1342.3 ($\text{M}^+ - 1$)
35 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{77}\text{N}_{11}\text{O}_{19}\text{S}_2 \cdot 12\text{H}_2\text{O}$:

C 47.72, H 6.52, N 9.87

Found: C 47.98, H 6.00, N 9.72

Example 147

5 IR (KBr): 2937, 1633, 1533, 1512, 1443 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8\text{Hz}$), 1.12 (3H, d,
J=5.6Hz), 1.60-2.64 (9H, m), 2.01 (2H, t, $J=6.3\text{Hz}$),
2.83-3.03 (3H, m), 3.13-3.60 (2H, m), 3.27 (3H, s),
3.50 (2H, t, $J=6.3\text{Hz}$), 3.68-4.58 (13H, m), 4.09
10 (2H, t, $J=6.4\text{Hz}$), 4.70-5.30 (8H, m), 6.71 (1H, d,
J=8.1Hz), 6.78 (1H, dd, $J=8.3$ and 7Hz), 7.01 (1H,
d, $J=1.6\text{Hz}$), 7.08 (2H, d, $J=8.8\text{Hz}$), 7.45 (1H, d,
J=8.4Hz), 7.57-7.82 (2H, m), 7.73 (2H, d, $J=8.8\text{Hz}$),
7.87 (2H, d, $J=8.5\text{Hz}$), 8.02-8.20 (6H, m), 8.30 (1H,
15 d, $J=6.2\text{Hz}$), 8.71 (1H, br s), 8.93 (1H, d, $J=7.4\text{Hz}$)

MASS (m/z): 1317.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{74}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 49.24, H 6.20, N 9.57

Found: C 48.95, H 6.04, N 9.36

Example 148

IR (KBr): 2929, 1633, 1608, 1518, 1444, 1419 cm^{-1}

NMR (DMSO- d_6 , δ): 0.86 (3H, d, $J=6.4\text{Hz}$), 0.98 (3H, d,
J=6.8Hz), 1.14-1.40 (5H, m), 1.11 (3H, d, $J=5.5\text{Hz}$),
25 1.60-2.74 (18H, m), 1.80-3.02 (3H, m), 3.02-3.58
(6H, m), 3.70-4.60 (13H, m), 4.70-5.40 (8H, m),
6.71 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, dd, $J=8.1$ and
1.6Hz), 7.01 (1H, d, $J=1.7\text{Hz}$), 7.08 (2H, d,
J=8.7Hz), 7.25 (1H, d, $J=8.8\text{Hz}$), 7.57-7.92 (2H, m),
30 7.45 (2H, d, $J=8.4\text{Hz}$), 8.00-8.20 (4H, m), 8.31 (1H,
d, $J=6.4\text{Hz}$), 8.71 (1H, br s), 8.91 (1H, d, $J=7.7\text{Hz}$)

MASS (m/z): 1333.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{82}\text{N}_{12}\text{O}_{18}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 48.92, H 6.73, N 11.22

Found: C 49.12, H 6.71, N 11.08

Example 149

IR (KBr): 2933, 2860, 1659, 1630, 1547, 1510, 1446,
1387, 1329 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d,
 $J=5.2\text{Hz}$), 1.26-1.60 (10H, m), 1.60-2.08 (5H, m),
2.18 (6H, s), 2.12-2.67 (4H, m), 2.79-3.03 (3H, m),
3.10-3.50 (12H, m), 3.21 (3H, s), 3.64 (2H, t,
 $J=6.2\text{Hz}$), 3.64-4.08 (6H, m), 4.12-4.52 (7H, m),
10 4.67-5.26 (8H, m), 6.65 (2H, s), 6.64-6.84 (2H, m),
6.94-7.10 (3H, m), 7.43 (1H, d, $J=8.8\text{Hz}$), 7.34-7.97
(2H, m), 7.80 (2H, d, $J=8.7\text{Hz}$), 8.22-8.40 (1H, m),
8.40-8.59 (1H, m), 8.72 (1H, br s)

MASS (m/z): 1325.6 (M^+-1)

15 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{90}\text{N}_{10}\text{O}_{20}\text{S}\cdot 6\text{H}_2\text{O}$:

C 51.87, H 7.16, N 9.76

Found: C 51.80, H 7.15, N 9.72

Example 150

20 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.9\text{Hz}$), 1.07 (3H, d,
 $J=5.2\text{Hz}$), 0.80-2.67 (21H, m), 2.77-3.00 (3H, m),
3.08-2.58 (10H, m), 3.52 (2H, t, $J=6.3\text{Hz}$), 3.68-
4.51 (16H, m), 4.70-5.28 (8H, m), 6.68-7.10 (9H,
m), 7.43 (1H, d, $J=8.8\text{Hz}$), 7.56-7.90 (2H, m), 7.80
25 (2H, d, $J=8.8\text{Hz}$), 8.26-8.40 (1H, m), 8.40-8.55 (1H,
m), 8.65-8.80 (1H, m)

MASS (m/z): 1309.5 (M^+-1)

Example 151

30 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.10 (3H, d,
 $J=6.0\text{Hz}$), 1.39 (9H, s), 1.65-2.83 (22H, m), 1.81-
3.06 (3H, m), 3.20-4.54 (18H, m), 4.69-5.34 (8H,
m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, dd, $J=8.3$ and
1.8Hz), 6.70-6.90 (1H, m), 6.98-7.14 (3H, m), 7.44
35 (1H, d, $J=8.8\text{Hz}$), 7.68 (2H, d, $J=8.7\text{Hz}$), 7.72 (2H,

d, $J=8.3\text{Hz}$), 7.38-7.86 (2H, m), 7.95 (2H, d, $J=8.5\text{Hz}$), 8.33 (1H, d, $J=6.8\text{Hz}$), 8.70 (1H, br s), 8.75 (1H, d, $J=7.7\text{Hz}$)

MASS (m/z): 1324.5 (M^+-1)

5

Example 152

IR (KBr): 1632, 1514, 1452, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-1.3 (12H, m), 1.5-2.6 (11H, m), 2.7-3.6 (18H, m), 3.6-5.3 (23H, m), 6.7-7.2 (9H, m), 7.4-7.55 (1H, m), 7.6-7.85 (7H, m), 7.94 (2H, d, $J=8.3\text{Hz}$), 8.2-8.4 (1H, m), 8.65-8.8 (1H, m)

10

MASS (m/z): 1266 (M^++23)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{11}\text{O}_{19}\text{S}\cdot 7\text{H}_2\text{O}$:

C 52.27, H 6.79, N 10.48

15

Found: C 52.00, H 6.61, N 10.42

Example 153

NMR (DMSO- d_6 , δ): 0.8-1.3 (6H, m), 1.4-2.6 (13H, m), 2.6-3.6 (15H, m), 3.7-5.3 (21H, m), 6.65-6.9 (2H, m), 6.96 (1H, s), 7.15 (2H, d, $J=8.3\text{Hz}$), 7.35-7.8 (7H, m), 7.86 (2H, d, $J=8.7\text{Hz}$), 7.9-8.2 (5H, m), 8.6-8.9 (2H, m)

20

MASS (m/z): 1376 (M^+-23)

25 Example 154

IR (KBr): 3380.6, 1645.0, 1631.5, 1608.3, 1538.9, 1515.8, 1442.5, 1419.4, 1268.9, 1240.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8\text{Hz}$), 1.11 (3H, d, $J=5.6\text{Hz}$), 1.2-5.4 (48H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.7-6.9 (1H, m), 7.01 (1H, d, $J=1.8\text{Hz}$), 7.07 (2H, d, $J=9.1\text{Hz}$), 7.45 (1H, d, $J=9.2\text{Hz}$), 7.5-7.9 (2H, m), 7.83 (2H, d, $J=8.9\text{Hz}$), 8.07 (4H, s), 8.30 (1H, d, $J=5.9\text{Hz}$), 8.5-8.8 (1H, m), 8.90 (1H, d, $J=7.8\text{Hz}$)

30

MASS (m/z): 1236.3 (M^--1)

35

Elemental Analysis Calcd. for $\text{C}_{55}\text{H}_{71}\text{N}_{11}\text{O}_{18}\text{S}_2\cdot 10\text{H}_2\text{O}$:

C 46.57, H 6.47, N 10.86

Found: C 46.74, H 6.12, N 10.75

Example 155

5 IR (KBr): 3359.4, 1645.0, 1631.5, 1538.9, 1515.8,
1438.6, 1255.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.91 (3H, t, $J=7.1\text{Hz}$), 0.97 (3H, d, $J=6.8\text{Hz}$), 1.10 (3H, d, $J=5.8\text{Hz}$), 1.2-5.4 (46H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 7.00 (1H,
10 d, $J=1.6\text{Hz}$), 7.08 (2H, d, $J=8.9\text{Hz}$), 7.45 (1H, d,
 $J=8.3\text{Hz}$), 7.5-8.1 (3H, m), 7.80 (2H, d, $J=8.4\text{Hz}$),
7.91 (2H, d, $J=8.8\text{Hz}$), 7.98 (2H, d, $J=8.5\text{Hz}$), 8.2
(1H, m), 8.39 (1H, s), 8.79 (1H, d, $J=7.9\text{Hz}$)

MASS (m/z): 1238.3 ($M^- - 1$)

15 Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{73}\text{N}_9\text{O}_{19}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 47.96, H 6.54, N 8.99

Found: C 48.14, H 6.36, N 8.90

Example 156

20 IR (KBr): 3355.5, 1635.3, 1529.3, 1517.7, 1434.8,
1255.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.87 (3H, t, $J=6.5\text{Hz}$), 0.97 (3H, d, $J=6.8\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.2-5.4 (52H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=9.9\text{Hz}$), 7.00
25 (1H, d, $J=1.6\text{Hz}$), 7.09 (2H, d, $J=9.0\text{Hz}$), 7.45 (1H,
d, $J=8.8\text{Hz}$), 7.5-7.9 (2H, m), 7.97 (2H, d,
 $J=8.5\text{Hz}$), 8.06 (2H, d, $J=8.5\text{Hz}$), 8.29 (1H, d,
 $J=8.9\text{Hz}$), 8.40 (2H, d, $J=8.8\text{Hz}$), 8.81 (1H, d,
 $J=7.4\text{Hz}$), 9.26 (2H, s)

30 MASS (m/z): 1275.4 ($M^- - 1$)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{80}\text{N}_{10}\text{O}_{19}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 50.70, H 6.81, N 9.85

Found: C 50.50, H 6.69, N 9.69

Example 157

IR (KBr): 3361.3, 1631.5, 1511.9, 1446.4, 1267.0,
1232.3, 1045.2 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d,
 $J=5.8\text{Hz}$), 1.0-5.6 (57H, m), 6.70 (1H, d, $J=8.1\text{Hz}$),
6.7-6.9 (1H, m), 6.92 (2H, d, $J=8.7\text{Hz}$), 6.99 (1H,
s), 7.01 (2H, d, $J=9.4\text{Hz}$) 7.09 (2H, d, $J=8.7\text{Hz}$),
7.3-7.9 (3H, m), 7.80 (2H, d, $J=8.8\text{Hz}$), 8.1-8.5
(3H, m)

10 MASS (m/z): 1235.4 (M^- -H)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{80}\text{N}_{10}\text{O}_{18}\text{S}\cdot 9\text{H}_2\text{O}$:

C 49.78, H 7.06, N 10.01

Found: C 49.88, H 6.87, N 9.89

15 Example 158

IR (KBr): 3359.4, 1633.4, 1535.1, 1511.9, 1442.5,
1251.6 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.8-1.1 (6H, m), 1.1-1.3 (3H, m),
1.3-5.6 (42H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.77 (1H,
d, $J=9.8\text{Hz}$), 6.97 (1H, s), 7.07 (2H, d, $J=8.9\text{Hz}$),
7.2-9.0 (15H, m)

MASS (m/z): 1287.4 (M^- -1)

Example 159

25 IR (KBr): 3359.4, 1631.5, 1610.3, 1538.9, 1502.3,
1450.2, 1230.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.0-1.3 (3H,
m), 1.3-5.8 (59H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.77
(1H, d, $J=9.9\text{Hz}$), 6.8-7.3 (8H, m), 7.3-9.2 (11H, m)

30 MASS (m/z): 1345.5 (M^- -1)

Example 160

MASS (m/z): 1222.3 (M^- -1)

Example 161

IR (KBr): 3353.6, 1631.5, 1537.0, 1517.7, 1467.6,
1440.6, 1272.8, 1045.2 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.7-1.0 (3H, m), 0.98 (3H, d,
J=6.8Hz), 1.11 (3H, d, J=5.6Hz), 1.2-5.5 (46H, m),
6.71 (1H, d, J=8.1Hz), 6.7-6.9 (1H, m), 7.00 (1H,
d, J=1.6Hz), 7.45 (1H, d, J=8.1Hz), 7.5-8.2 (13H,
m), 8.30 (1H, d, J=7.6Hz), 8.77 (1H, d, J=7.1Hz)

MASS (m/z): 1256.4 (M^- -1)

10 Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{75}\text{N}_9\text{O}_{19}\text{S}\cdot 8\text{H}_2\text{O}$:

C 51.38, H 6.54, N 8.99

Found: C 51.15, H 6.41, N 8.76

Example 162

15 IR (KBr): 3425.0, 3396.0, 3365.2, 1631.5, 1537.0,
1510.0, 1450.2, 1286.3, 1267.0, 1234.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=5.7Hz), 1.3-5.6 (63H, m), 6.7-7.2 (9H, m), 7.3-
7.8 (3H, m), 7.80 (2H, d, J=8.8Hz), 8.0-8.5 (2H, m)

20 MASS (m/z): 1313.4 (M^- -1)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{86}\text{N}_{10}\text{O}_{21}\text{S}\cdot 10\text{H}_2\text{O}$:

C 48.19, H 7.14, N 9.37

Found: C 48.45, H 6.94, N 9.32

25 Example 163

IR (KBr): 1469, 1541, 1514 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.6 (11H, m), 1.6-2.7 (15H, m),
2.7-3.6 (8H, m), 3.6-5.3 (21H, m), 6.7-6.9 (2H, m),
7.00 (1H, s), 7.2-7.9 (5H, m), 7.96 (2H, d,
30 J=8.3Hz), 8.0-8.4 (5H, m), 8.6-9.0 (2H, m)

MASS (m/z): 1235 (M^+ -1)

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{72}\text{N}_{10}\text{O}_{18}\text{S}_2\cdot 7\text{H}_2\text{O}$:

C 49.33, H 6.36, N 10.27

Found: C 49.07, H 6.40, N 10.02

Example 164

IR (KBr): 1633, 1516, 1444, 1255 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-2.6 (25H, m), 2.7-3.6 (8H, m),
3.6-5.3 (22H, m), 6.65-6.85 (2H, m), 7.00 (1H, s),
5 7.14 (2H, d, $J=9.0\text{Hz}$), 7.4-8.2 (10H, m), 8.2-8.4
(1H, m), 8.8-9.0 (1H, m)

MASS (m/z): 1251 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{72}\text{N}_{10}\text{O}_{19}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 48.13, H 6.35, N 10.02

10 Found: C 48.26, H 6.35, N 9.80

Example 165

IR (KBr): 1633, 1518, 1444, 1250 cm^{-1}

15 NMR (DMSO- d_6 , δ): 0.8-1.6 (15H, m), 1.6-2.6 (11H, m),
2.7-3.6 (8H, m), 3.6-5.3 (23H, m), 6.65-6.85 (2H,
m), 7.00 (1H, s), 7.10 (2H, d, $J=9.0\text{Hz}$), 7.3-8.4
(12H, m), 8.8-9.0 (1H, m), 9.23 (1H, s)

MASS (m/z): 1365 (M^++23)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{76}\text{N}_{12}\text{O}_{19}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

20 C 47.77, H 6.39, N 11.33

Found: C 47.67, H 6.19, N 11.20

Example 166

IR (KBr): 1662, 1635, 1605, 1444 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.8-1.4 (6H, m), 1.5-2.6 (13H, m),
2.6-3.6 (11H, m), 3.6-5.3 (23H, m), 6.65-6.85 (2H,
m), 6.99 (1H, s), 7.05-8.4 (18H, m), 8.8-9.0 (1H,
m)

MASS (m/z): 1312 (M^+-1)

30 Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{75}\text{N}_{11}\text{O}_{18}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 49.62, H 6.35, N 10.43

Found: C 49.73, H 6.16, N 10.27

Example 167

IR (KBr): 1659, 1628, 1605, 1444 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-2.7 (29H, m), 2.7-5.3 (35H, m),
6.65-6.85 (2H, m), 6.9-7.2 (3H, m), 7.3-7.95 (5H,
5 m), 8.0-8.4 (6H, m), 8.8-9.0 (1H, m)

MASS (m/z): 1334 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{81}\text{N}_{11}\text{O}_{19}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 48.89, H 6.66, N 10.28

Found: C 48.83, H 6.45, N 10.11

10

Example 168

IR (KBr): 1659, 1628, 1444 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-2.7 (34H, m), 3.8-3.6 (8H, m),
3.6-5.3 (23H, m), 6.65-6.85 (2H, m), 6.99 (1H, s),
15 7.3-7.85 (5H, m), 7.9-8.4 (7H, m), 8.57 (1H, s),
8.8-9.0 (1H, m)

MASS (m/z): 1283 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{57}\text{H}_{80}\text{N}_{12}\text{O}_{18}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 47.89, H 6.77, N 11.76

Found: C 47.65, H 6.63, N 11.53

20

Example 169

IR (KBr): 3324, 2937, 1658, 1629, 1529, 1517, 1465,
1446, 1255, 1178, 1112, 1085, 1045 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.3-1.6 (4H, m), 1.6-2.1 (4H, m), 2.1-2.5
(3H, m), 2.9 (3H, m), 3.23 (1H, s), 3.38 (2H, m),
3.7-4.6 (19H, m), 4.8 (4H, m), 5.2 (3H, m), 6.71
(1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=8.2\text{Hz}$), 7.00 (1H,
30 s), 7.15 (2H, d, $J=8.8\text{Hz}$), 7.44 (1H, d, $J=8.5\text{Hz}$),
7.6-7.8 (3H, m), 7.67 (1H, m), 7.90 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (4H, s), 8.34 (1H, d, $J=7.1\text{Hz}$), 8.75
(1H, d, $J=7.5\text{Hz}$), 8.86 (1H, s)

MASS (m/z): 1308.3 (M^++1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{75}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

35

C 47.89, H 6.31, N 10.59
Found: C 48.02, H 6.21, N 10.49

Example 170

5 IR (KBr): 3300, 1635.3, 1510.0, 1232.3 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d,
 $J=5.3\text{Hz}$), 1.72-5.21 (58H, m), 6.69-8.67 (20H, m)
MASS (m/z): 1377.4 ($\text{M}^+ + \text{Na}$)
Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{84}\text{ClN}_{11}\text{O}_{19}\text{S}\cdot 6\text{H}_2\text{O}$:
10 C 51.69, H 6.51, N 10.36
Found: C 51.74, H 6.54, N 10.59

Example 171

15 IR (KBr): 3347.8, 1631.5, 1610.3, 1510.0, 1230.4 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.9\text{Hz}$), 1.08 (3H, d,
 $J=4.6\text{Hz}$), 1.70-5.40 (55H, m), 6.67-8.71 (22H, m)
MASS (m/z): 1313.4
Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{83}\text{N}_{11}\text{O}_{18}\text{S}\cdot 4\text{H}_2\text{O}$:
C 54.57, H 6.61, N 11.11
20 Found: C 54.32, H 6.64, N 11.00

Example 172

25 IR (KBr): 1659, 1635, 1606, 1529, 1446, 1242 cm^{-1}
NMR (DMSO- d_6 , δ): 0.8-1.3 (12H, m), 1.4-2.6 (11H, m),
2.7-3.6 (8H, m), 3.6-5.3 (25H, m), 6.1-6.85 (2H,
m), 6.99 (1H, s), 7.11 (2H, d, $J=8.7\text{Hz}$), 7.4-7.85
(3H, m), 7.87 (2H, d, $J=8.9\text{Hz}$), 8.0-8.4 (6H, m),
8.8 (1H, m)
MASS (m/z): 1266 ($\text{M}^+ - 1$)
30 Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{73}\text{N}_{11}\text{O}_{19}\text{S}_2\cdot 10\text{H}_2\text{O}$:
C 46.43, H 6.47, N 10.64
Found: C 46.45, H 5.95, N 10.46

Example 173

IR (KBr): 1659, 1635, 1612, 1512, 1446, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-1.3 (12H, m), 1.5-2.4 (11H, m),
2.7-3.6 (18H, m), 3.6-5.3 (23H, m), 6.6-7.1 (9H,
5 m), 7.3-7.9 (6H, m), 8.2-8.5 (2H, m)

MASS (m/z): 1266 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{81}\text{N}_{11}\text{O}_{19}\text{S}\cdot 7\text{H}_2\text{O}$:

C 49.96, H 6.87, N 11.05

Found: C 49.78, H 6.64, N 10.93

10

Example 174

IR (KBr): 1659, 1628, 1510, 1446, 1236 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.5 (22H, m), 1.5-2.6 (16H, m),
2.7-3.6 (12H, m), 3.6-5.3 (21H, m), 6.6-7.05 (5H,
15 m), 7.3-7.9 (6H, m), 8.2-8.5 (2H, m)

MASS (m/z): 1215 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{84}\text{N}_{10}\text{O}_{18}\text{S}\cdot 7\text{H}_2\text{O}$:

C 50.06, H 7.35, N 10.43

Found: C 49.95, H 7.19, N 10.30

20

Example 175

IR (KBr): 1630, 1510, 1446, 1238 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.4 (20H, m), 1.6-2.75 (18H, m),
2.75-3.7 (12H, m), 3.7-4.55 (13H, m), 4.6-5.3 (8H,
25 m), 6.6-7.1 (5H, m), 7.3-7.9 (5H, m), 8.2-8.6 (2H,
m), 8.71 (1H, s)

MASS (m/z): 1215 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{84}\text{N}_{10}\text{O}_{18}\text{S}\cdot 8\text{H}_2\text{O}$:

C 49.40, H 7.40, N 10.29

Found: C 49.45, H 7.28, N 10.20

30

Example 176

IR (KBr): 1664, 1635, 1446, 1240 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.3 (6H, m), 1.4-2.65 (15H, m),
35 2.7-3.6 (12H, m), 3.65-5.3 (21H, m), 6.65-6.85 (2H,

m), 6.9-7.2 (3H, m), 7.3-7.85 (5H, m), 7.9-8.4 (7H, m), 8.7-8.95 (1H, m), 9.17 (1H, s)

MASS (m/z): 1303 (M^+)

Elemental Analysis Calcd. for $C_{58}H_{73}N_{13}O_{18}S \cdot 7H_2O$:

5 C 48.70, H 6.13, N 12.73
Found: C 48.48, H 5.79, N 12.45

Example 177

IR (KBr): 1649, 1632, 1539, 1512, 1454, 1238 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.8-2.75 (39H, m), 2.75-5.3 (36H, m),
6.65-7.05 (5H, m), 7.3-7.9 (5H, m), 8.2-8.6 (2H, m), 8.71 (1H, s)

MASS (m/z): 1271 (M^+-1)

Elemental Analysis Calcd. for $C_{59}H_{88}N_{10}O_{19}S \cdot 7H_2O$:

15 C 49.99, H 7.39, N 9.88
Found: C 49.80, H 7.21, N 10.11

Example 178

IR (KBr): 1651, 1541, 1512, 1232 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.8-1.2 (9H, m), 1.4-2.1 (12H, m),
2.1-3.6 (26H, m), 3.6-4.5 (13H, m), 4.6-5.3 (8H, m), 6.6-7.1 (9H, m), 7.3-7.9 (5H, m), 8.2-8.8 (3H, m)

MASS (m/z): 1310 (M^+-1)

25 Elemental Analysis Calcd. for $C_{56}H_{84}N_{10}O_{18}S \cdot 7H_2O$:

C 50.09, H 6.94, N 10.71
Found: C 49.86, H 6.80, N 10.65

Example 179

30 IR (KBr): 1649, 1632, 1539, 1512, 1454, 1238 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-2.7 (39H, m), 2.7-5.3 (36H, m),
6.65-7.1 (5H, m), 7.3-7.8 (5H, m), 8.25-8.55 (2H, m), 8.70 (1H, s)

MASS (m/z): 1273 (M^++1)

35 Elemental Analysis Calcd. for $C_{59}H_{88}N_{10}O_{19}S \cdot 7H_2O$:

C 50.63, H 7.35, N 10.01

Found: C 50.54, H 7.24, N 9.87

Example 180

5 IR (KBr): 1649, 1632, 1541, 1506, 1454, 1232 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-1.3 (12H, m), 1.6-2.6 (11H, m),
2.6-5.3 (41H, m), 6.7-7.2 (9H, m), 7.3-7.9 (10H,
m), 8.2-8.6 (2H, m)

MASS (m/z): 1342 (M^+-1)

10 Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{11}\text{O}_{19}\text{S}\cdot 10\text{H}_2\text{O}$:

C 50.42, H 6.94, N 10.11

Found: C 50.71, H 6.82, N 10.03

Example 181

15 IR (KBr): 3353.6, 1633.4, 1537.0, 1508.1, 1438.6,
1257.4, 1045.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.91 (3H, t, $J=7.1\text{Hz}$), 0.98 (3H, d,
 $J=6.8\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.2-5.6 (45H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=10.0\text{Hz}$), 7.00
20 (1H, s), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.45 (1H, d,
 $J=8.8\text{Hz}$), 7.54 (1H, s), 7.6-8.0 (2H, m), 7.85 (2H,
d, $J=8.7\text{Hz}$), 7.99 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d,
 $J=8.6\text{Hz}$), 8.31 (1H, d, $J=7.1\text{Hz}$), 8.71 (1H, s), 8.87
(1H, d, $J=7.1\text{Hz}$)

25 MASS (m/z): 1222.3 (M^--1)

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{73}\text{N}_9\text{O}_{20}\text{S}\cdot 7\text{H}_2\text{O}$:

C 49.81, H 6.49, N 9.33

Found: C 49.99, H 6.43, N 9.30

30 Example 182

IR (KBr): 3374.8, 1658.5, 1627.6, 1529.3, 1517.7,
1486.8, 1446.4, 1276.6, 1247.7 cm^{-1}

NMR (DMSO- d_6 , δ): 0.91 (3H, t, $J=7.1\text{Hz}$), 0.97 (3H, d,
 $J=6.9\text{Hz}$), 1.12 (3H, d, $J=5.8\text{Hz}$), 1.2-6.5 (46H, m),

35 6.71 (1H, d, $J=8.1\text{Hz}$), 6.77 (1H, d, $J=10.0\text{Hz}$), 6.99

(1H, d, J=1.6Hz), 7.20 (2H, d, J=8.9Hz), 7.46 (1H, d, J=9.5Hz), 7.5-8.3 (3H, m), 8.08 (2H, d, J=8.6Hz), 8.14 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.4Hz), 8.3-8.8 (1H, m), 8.84 (1H, d, J=7.2Hz)

5 MASS (m/z): 1231.3 (M^{-1})

Elemental Analysis Calcd. for $C_{59}H_{72}N_9NaO_{20}S \cdot 7H_2O$:

C 49.81, H 6.49, N 9.33

Found: C 49.99, H 6.43, N 9.30

10 Example 183

IR (KBr): 3353.6, 1633.4, 1538.9, 1502.3, 1461.8, 1444.4, 1259.3, 1045.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.91 (3H, t, J=7.1Hz), 0.97 (3H, d, J=7.0Hz), 1.11 (3H, d, J=5.7Hz), 1.2-6.5 (45H, m),
15 6.71 (1H, d, J=8.2Hz), 6.7-6.9 (1H, m), 6.99 (1H, d, J=1.7Hz), 7.04 (2H, d, J=8.8Hz), 7.45 (1H, d, J=9.0Hz), 7.5-7.9 (10H, m), 8.00 (2H, d, J=8.4Hz), 8.26 (1H, d, J=7.1Hz), 8.3-8.7 (1H, m), 8.73 (1H, d, J=7.9Hz)

20 MASS (m/z): 1223.3 (M^{-1})

Elemental Analysis Calcd. for $C_{59}H_{76}N_8O_{19}S \cdot 6H_2O$:

C 52.83, H 6.61, N 8.35

Found: C 59.91, H 6.54, N 8.32

25 Example 184

IR (KBr): 3353.6, 1658.5, 1633.4, 1232.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.7Hz), 1.50-5.30 (56H, m), 6.68-8.40 (23H, m)

MASS (m/z): 1342.3 (M^{+1})

30 Elemental Analysis Calcd. for $C_{64}H_{85}N_{11}O_{19}S \cdot 7H_2O$:

C 52.27, H 6.79, N 10.48

Found: C 51.98, H 6.47, N 10.59

Example 185IR (KBr): 3347.8, 1633.4, 1511.9, 1230.4 cm^{-1} NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.07 (3H, d, $J=5.0\text{Hz}$), 1.20-5.22 (66H, m), 6.64-8.56 (17H, m)5 MASS (m/z): 1334.5 (M^++1)Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{89}\text{N}_{11}\text{O}_{19}\text{S}\cdot 7\text{H}_2\text{O}$:

C 51.74, H 7.10, N 10.53

Found: C 52.06, H 6.95, N 10.49

10 Example 186IR (KBr): 3365.2, 1664.3, 1633.4, 1230.4 cm^{-1} NMR (DMSO- d_6 , δ): 0.81-5.25 (78H, m), 6.67-8.53 (14H, m)Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{92}\text{N}_{10}\text{O}_{19}\text{S}\cdot 12\text{H}_2\text{O}$:

C 48.28, H 7.70, N 9.23

15 Found: C 48.02, H 6.69, N 9.39

Example 187IR (KBr): 3350. 1631.5, 1511.9, 1232.3 cm^{-1} NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.09 (3H, d, $J=6.0\text{Hz}$), 1.42-5.20 (61H, m), 6.68-8.40 (18H, m)20 MASS (m/z): 1292.3 (M^++1)Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{85}\text{N}_{11}\text{O}_{18}\text{S}\cdot 7\text{H}_2\text{O}$:

C 51.65, H 7.03, N 10.86

Found: C 51.72, H 6.86, N 10.86

25

Example 188IR (KBr): 1658.5, 1629.6, 1511.9, 1232.3 cm^{-1} NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.5\text{Hz}$), 1.11 (3H, d, $J=5.1\text{Hz}$), 1.51-5.19 (58H, m), 6.68-8.29 (17H, m)30 MASS (m/z): 1294.4 (M^+-1)Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{81}\text{N}_{11}\text{O}_{20}\text{S}\cdot 7\text{H}_2\text{O}$:

C 49.82, H 6.73, N 10.83

Found: C 50.33, H 6.42, N 11.00

Example 189

IR (KBr): 3328, 2940, 1664, 1629, 1529, 1519, 1467,
1446, 1257, 1178, 1112, 1085, 1047 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.5-2.1 (11H, m), 2.2-2.5 (5H, m), 2.90
(3H, m), 3.24 (3H, s), 3.38 (2H, m), 3.4 (2H, m),
3.6-4.6 (18H, m), 4.6-4.9 (3H, m), 5.20 (2H, m),
6.70 (1H, d, $J=8.2\text{Hz}$), 6.80 (1H, d, $J=8.2\text{Hz}$), 7.00
10 (1H, s), 7.15 (2H, d, $J=8.8\text{Hz}$), 7.45 (1H, d,
 $J=8.0\text{Hz}$), 7.7 (3H, m), 7.90 (2H, d, $J=8.8\text{Hz}$), 7.96
(4H, s), 8.3 (1H, m), 8.70 (1H, d, $J=7.8\text{Hz}$), 8.85
(1H, s)

MASS (m/z): 1294.3 (M^+-1)

15 Example 190

IR (KBr): 3324, 2937, 1658, 1635, 1529, 1517, 1465,
1446, 1257, 1178, 1114, 1087, 1045 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.2-1.6 (6H, m), 1.6-2.1 (4H, m), 2.1-2.5
(3H, m), 2.9 (3H, m), 3.22 (3H, s), 3.38 (2H, m),
3.6-4.3 (14H, m), 4.3-4.6 (5H, m), 4.6-4.9 (4H, m),
5.2 (3H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d,
 $J=8.2\text{Hz}$), 7.00 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.44
(1H, d, $J=8.2\text{Hz}$), 7.6-7.8 (3H, m), 7.90 (2H, d,
25 $J=8.8\text{Hz}$), 7.96 (4H, s), 8.33 (1H, d, $J=7.1\text{Hz}$), 8.74
(1H, d, $J=7.7\text{Hz}$), 8.86 (1H, s)

MASS (m/z): 1322.4 (M^+-1)

Example 191

30 IR (KBr): 2937, 2864, 1659, 1632, 1510, 1446, 1387,
1327 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d,
 $J=5.8\text{Hz}$), 1.22-2.60 (17H, m), 2.79-3.03 (3H, m),
3.10-3.55 (12H, m), 3.21 (3H, s), 3.64-4.08 (6H,
35 m), 3.85 (2H, t, $J=6.5\text{Hz}$), 4.12-4.52 (7H, m), 4.67-

4.90 (6H, m), 5.10-5.25 (2H, m), 6.65-7.08 (9H, m),
7.43 (1H, d, $J=8.2\text{Hz}$), 7.53-7.88 (2H, m), 7.80 (2H,
d, $J=8.8\text{Hz}$), 8.27 (2H, d, $J=7.8\text{Hz}$), 8.44 (1H, d,
 $J=7.6\text{Hz}$)

5 MASS (m/z): 1283.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{84}\text{N}_{10}\text{O}_{20}\text{S}\cdot 5\text{H}_2\text{O}$:

C 51.52, H 6.89, N 10.18

Found: C 51.51, H 6.96, N 10.09

10 Example 192

IR (KBr): 2935, 2856, 1633, 1533, 1518, 1497, 1446,
1385 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.4\text{Hz}$), 1.05-1.38 (6H, m), 1.50-2.14 (9H, m),
15 2.14-2.43 (2H, m), 2.43-2.67 (7H, m), 2.79-3.03
(3H, m), 3.10-3.50 (6H, m), 3.64-4.08 (6H, m),
4.12-4.52 (7H, m), 4.67-5.26 (8H, m), 6.67-6.84
(2H, m), 6.96-7.10 (1H, m), 7.02 (2H, d, $J=8.8\text{Hz}$),
7.44 (1H, d, $J=8.9\text{Hz}$), 7.61 (2H, d, $J=8.8\text{Hz}$), 7.52-
20 7.50 (2H, m), 7.70 (2H, d, $J=8.2\text{Hz}$), 7.93 (2H, d,
 $J=8.4\text{Hz}$), 8.26-8.40 (1H, m), 8.68-8.84 (2H, m)

MASS (m/z): 1235.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{80}\text{N}_{10}\text{O}_{18}\text{S}\cdot 7\text{H}_2\text{O}$:

C 51.09, H 6.95, N 10.27

25 Found: C 50.78, H 6.88, N 10.10

Example 193

To a solution of the starting compound (193) (21 mg) in
methanol (1 ml) was added a solution of hydrogen chloride in
30 methanol (0.5 ml), and stirred for 4 hours at ambient
temperature. The reaction mixture was diluted with water,
and subjected to column chromatography on ODS (YMC-gel ODS-
AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.))
eluting with 20% acetonitrile aqueous solution. The
35 fractions containing the object compound were combined, and

evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (193) (19 mg).

IR (KBr): 3355, 2935, 1658, 1635, 1529, 1446, 1255,
5 1180, 1083, 1006 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.04 (3H, d, $J=5.7\text{Hz}$), 1.2-1.6 (8H, m), 1.6-2.6 (13H, m), 2.6-3.8 (5H, m), 3.10 (9H, s), 3.21 (3H, s), 3.30 (4H, t, $J=6.4\text{Hz}$), 3.8-4.7 (12H, m), 4.7-5.0 (3H, m), 5.2
10 (3H, m), 5.74 (1H, m), 6.38 (1H, d, $J=8.2\text{Hz}$), 6.59 (1H, s), 6.60 (1H, d, $J=8.2\text{Hz}$), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.37 (1H, d, $J=9.2\text{Hz}$), 7.53 (1H, d, $J=9.2\text{Hz}$), 7.84 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.06 (2H, d, $J=8.8\text{Hz}$), 8.11 (2H, d, $J=8.8\text{Hz}$), 8.67 (2H, d, $J=4.0\text{Hz}$), 8.85 (1H, d, $J=8.2\text{Hz}$), 8.91 (1H, d, $J=8.2\text{Hz}$)
15

MASS (m/z): 1261.5 (M^+)

The following compounds [Examples 194 to 206] were
20 obtained according to a similar manner to that of Example 193.

Example 194

IR (KBr): 3353, 2937, 1664, 1627, 1606, 1529, 1446,
25 1255, 1178, 1112, 1087, 1066, 1006 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.7\text{Hz}$), 1.2-1.6 (12H, m), 1.6-3.8 (23H, m), 3.21 (3H, s), 3.28 (4H, t, $J=6.4\text{Hz}$), 3.8-4.25 (9H, m), 4.25-4.6 (4H, m), 4.8 (4H, m), 5.1 (1H, m), 5.18
30 (1H, d, $J=3.0\text{Hz}$), 5.23 (1H, d, $J=5.6\text{Hz}$), 5.40 (1H, m), 6.39 (1H, d, $J=8.0\text{Hz}$), 6.57 (1H, m), 6.61 (1H, d, $J=8.0\text{Hz}$), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.42 (1H, d, $J=8.8\text{Hz}$), 7.55 (1H, m), 7.80 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.07 (2H, d, $J=8.8\text{Hz}$), 8.12 (2H, d, $J=8.8\text{Hz}$), 8.57 (1H, d, $J=7.8\text{Hz}$), 8.68 (2H, s), 8.89
35

(1H, d, J=7.3Hz)

MASS (m/z): 1290.4 (M^+ +1)

Example 195

5 IR (KBr): 3353, 2935, 1658, 1635, 1606, 1529, 1446,
1255, 1180, 1114, 1085, 1062, 1004 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d,
J=5.7Hz), 1.2-1.6 (10H, m), 1.6-2.6 (21H, m), 2.6-
3.8 (7H, m), 3.21 (3H, s), 3.30 (4H, t, J=6.4Hz),
10 3.8-4.5 (11H, m), 4.8 (3H, m), 5.05 (1H, m), 5.2-
5.3 (2H, m), 5.38 (1H, m), 6.39 (1H, d, J=8.0Hz),
6.57 (1H, m), 6.60 (1H, d, J=8.0Hz), 7.14 (2H, d,
J=8.8Hz), 7.41 (1H, d, J=8.7Hz), 7.45 (1H, d,
J=8.7Hz), 7.87 (1H, d, J=6.8Hz), 7.97 (2H, d,
J=8.8Hz),
15 8.06 (2H, d, J=8.8Hz), 8.12 (21H, d,
J=8.8Hz), 8.60 (1H, d, J=8.0Hz), 8.67 (2H, s), 8.88
(1H, d, J=7.5Hz)

MASS (m/z): 1302.4 (M^+ +1)

20 Example 196

IR (KBr): 3353, 2937, 1664, 1627, 1529, 1446, 1255,
1180, 1114, 1087, 1064, 1006 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=5.7Hz), 1.2-1.6 (8H, m), 1.6-2.7 (15H, m), 2.7-
25 3.6 (5H, m), 3.21 (3H, s), 3.6-4.25 (12H, m), 4.25-
4.6 (4H, m), 4.6-5.0 (3H, m), 5.11 (2H, m), 5.35
(1H, m), 6.39 (1H, d, J=8.0Hz), 6.57 (1H, m), 6.61
(1H, d, J=8.0Hz), 7.05 (2H, m), 7.14 (2H, d,
J=8.8Hz), 7.22 (1H, m), 7.44 (1H, d, J=8.9Hz), 7.6-
30 7.8 (2H, m), 7.97 (2H, d, J=8.8Hz), 8.04 (2H, d,
J=8.8Hz), 8.11 (2H, d, J=8.8Hz), 8.39 (1H, d,
J=7.5Hz), 8.68 (1H, m), 8.90 (1H, d, J=6.9Hz)

MASS (m/z): 1261.4 (M^+ +1)

Example 197

IR (KBr): 3349, 2935, 1658, 1635, 1529, 1446, 1255,
1180, 1114, 1087, 1062, 1006 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d,
 $J=5.7\text{Hz}$), 1.3-1.6 (8H, m), 1.6-2.6 (15H, m), 2.6-
3.6 (8H, m), 3.21 (3H, s), 3.6-4.3 (12H, m), 4.40
(2H, m), 4.55 (1H, m), 4.65 (1H, m), 4.8 (3H, m),
5.16 (3H, m), 6.39 (1H, d, $J=8.0\text{Hz}$), 6.57 (1H, m),
10 6.62 (1H, d, $J=8.0\text{Hz}$), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.34
(1H, m), 7.51 (1H, d, $J=9.2\text{Hz}$), 7.68 (2H, m), 7.97
(2H, d, $J=8.8\text{Hz}$), 8.04 (2H, d, $J=8.8\text{Hz}$), 8.11 (2H,
d, $J=8.8\text{Hz}$), 8.20 (1H, d, $J=6.7\text{Hz}$), 8.57 (1H, m),
8.68 (2H, m), 8.86 (1H, d, $J=7.6\text{Hz}$), 9.14 (1H, s),
9.40 (1H, m)
15 MASS (m/z): 1303.3 (M^++1)

Example 198

IR (KBr): 3353.6, 1658.5, 1635.3, 1529.3, 1444.4,
1255.4 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8\text{Hz}$), 1.08 (3H, d,
 $J=5.6\text{Hz}$), 1.2-5.6 (68H, m), 6.40 (1H, d, $J=8.0\text{Hz}$),
6.58 (1H, s), 6.60 (1H, d, $J=8.1\text{Hz}$), 7.14 (2H, d,
 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (2H, d,
 $J=10.8\text{Hz}$), 8.13 (2H, d, $J=8.9\text{Hz}$), 7.3-9.2 (7H, m)
25 MASS (m/z): 1330.4 ($M^+-\text{Cl}$)

Example 199

IR (KBr): 3349, 2937, 1658, 1627, 1604, 1529, 1446,
1255, 1201, 1114, 1083, 1062, 1006 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.1-1.5 (10H, m), 1.6-2.6 (17H, m), 2.6-
3.8 (12H, m), 3.8-4.3 (10H, m), 4.4 (4H, m), 4.78
(2H, m), 5.3 (1H, m), 6.39 (1H, d, $J=8.0\text{Hz}$), 6.57
(1H, m), 6.60 (1H, d, $J=8.0\text{Hz}$), 7.20 (2H, d,
35 $J=9.0\text{Hz}$), 7.45 (1H, m), 7.73 (3H, m), 7.86 (2H, d,

J=8.8Hz), 7.97 (4H, s), 8.42 (1H, d, J=6.7Hz), 8.73 (1H, d, J=6.7Hz), 8.84 (1H, s), 10.35 (1H, m)

MASS (m/z): 1280.4 (M^+ +1)

5 Example 200

IR (KBr): 3349, 2935, 1658, 1627, 1606, 1529, 1446, 1251, 1201, 1114, 1085, 1064, 1006 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.7Hz), 1.1-1.7 (7H, m), 1.7-2.7 (15H, m), 2.7-3.8 (15H, m), 3.8-4.3 (12H, m), 4.45 (4H, m), 4.75 (2H, m), 5.42 (1H, m), 6.39 (1H, d, J=8.0Hz), 6.57 (1H, m), 6.60 (1H, d, J=8.0Hz), 7.18 (2H, d, J=9.0Hz), 7.45 (1H, d, J=8.6Hz), 7.73 (3H, m), 7.92 (2H, d, J=8.8Hz), 8.08 (4H, s), 8.41 (1H, d, J=6.7Hz), 8.89 (1H, d, J=6.7Hz), 10.6 (1H, m)

15 MASS (m/z): 1241.5 (M^+ +1)

Example 201

20 IR (KBr): 3347, 2937, 1658, 1635, 1531, 1506, 1444, 1255, 1180, 1114, 1085, 1060, 1006 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.0 (6H, m), 1.10 (3H, d, J=5.7Hz), 1.2-1.6 (5H, m), 1.6-2.7 (11H, m), 2.7-3.1 (4H, m), 3.1-4.3 (12H, m), 4.3-4.6 (5H, m), 4.6-4.9 (4H, m), 4.9-5.4 (5H, m), 6.39 (1H, d, J=8.2Hz), 6.56 (1H, s), 6.61 (1H, d, J=8.2Hz), 7.13 (2H, d, J=8.8Hz), 7.40 (1H, m), 7.3-7.5 (2H, m), 7.74 (1H, m), 7.85 (2H, d, J=8.8Hz), 8.00 (2H, d, J=8.8Hz), 8.06 (2H, d, J=8.8Hz), 8.41 (1H, m), 8.69 (2H, m), 8.88 (1H, d, J=7.0Hz)

30 MASS (m/z): 1144.3 (M^+ +1)

Example 202

IR (KBr): 3322, 2935, 1664, 1627, 1606, 1529, 1446, 1255, 1201, 1114, 1085, 1064, 1006 cm^{-1}

35 NMR (DMSO- d_6 , δ): 0.88 (3H, d, J=7.0Hz), 0.97 (3H, d,

J=6.7Hz), 1.10 (3H, d, J=5.7Hz), 0.8-1.2 (2H, m),
1.2-1.6 (5H, m), 1.6-2.0 (6H, m), 2.0-2.7 (9H, m),
2.7-3.1 (4H, m), 3.1-3.8 (9H, m), 3.8-4.3 (8H, m),
4.3-4.6 (4H, m), 4.6-4.9 (3H, m), 4.95 (1H, m),
5
5.12 (1H, d, J=7.3Hz), 5.3-5.4 (3H, m), 6.39 (1H,
d, J=8.0Hz), 6.57 (1H, s), 6.61 (1H, d, J=8.0Hz),
7.19 (2H, d, J=8.9Hz), 7.44 (1H, d, J=9.8Hz), 7.7
(1H, m), 7.93 (2H, d, J=8.8Hz), 8.08 (4H, s), 8.41
(1H, m), 8.70 (2H, s), 8.91 (1H, d, J=6.6Hz), 10.10
10 (1H, m)
MASS (m/z): 1255.4 (M^+ +1)

Example 203

IR (KBr): 3344, 2940, 1658, 1627, 1531, 1496, 1246,
15 1180, 1114, 1083, 1062, 1004 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d,
J=5.7Hz), 1.1-1.5 (8H, m), 1.65 (2H, m), 1.7-2.0
(6H, m), 2.1-2.7 (7H, m), 2.8-3.1 (4H, m), 3.1-3.8
(9H, m), 3.97 (7H, m), 4.16 (2H, d, J=6.5), 4.23
20 (1H, m), 4.4 (5H, m), 4.75 (3H, m), 4.98 (1H, m),
5.27 (1H, m), 6.39 (1H, d, J=8.0Hz), 6.57 (1H, m),
6.61 (1H, d, J=8.0Hz), 7.12 (2H, d, J=8.8Hz), 7.44
(1H, d, J=8.8Hz), 7.68 (2H, d, J=8.8Hz), 7.72 (2H,
d, J=8.8Hz), 7.6-7.9 (3H, m), 7.96 (2H, d,
25 J=8.8Hz), 8.42 (1H, m), 8.74 (1H, d, J=6.8Hz),
10.06 (1H, m)
MASS (m/z): 1157.6 (M^+ +1)

Example 204

30 IR (KBr): 3320, 2933, 1658, 1629, 1610, 1510, 1446,
1255, 1234, 1114, 1087, 1064, 1006 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.06 (3H, d,
J=5.7Hz), 1.2-1.5 (11H, m), 1.5-1.8 (3H, m), 1.8-
2.1 (5H, m), 2.1-2.7 (6H, m), 2.8-3.1 (4H, m), 3.1-
35 3.8 (13H, m), 3.21 (3H, s), 3.8-4.1 (7H, m), 3.90

- (2H, d, J=6.4Hz), 3.95 (1H, m), 4.2-4.5 (5H, m),
4.75 (3H, m), 5.24 (1H, m), 6.39 (1H, d, J=8.0Hz),
6.57 (1H, m), 6.60 (1H, d, J=8.0Hz), 6.91 (2H, d,
J=8.8Hz), 7.03 (2H, d, J=8.8Hz), 7.17 (1H, m), 7.42
5 (1H, d, J=8.4Hz), 7.72 (5H, m), 7.83 (2H, d,
J=8.4Hz), 8.43 (1H, m), 8.50 (1H, d, J=6.7Hz)
MASS (m/z): 1233.4 ($M^{+}+1$)

Example 205

- 10 IR (KBr): 1651, 1539, 1514, 1234 cm^{-1}
NMR (DMSO- d_6 , δ): 0.85 (9H, s), 0.8-1.3 (11H, m),
1.3-2.4 (13H, m), 2.4-5.4 (40H, m), 6.39 (1H, d,
J=7.5Hz), 6.5-6.7 (2H, m), 7.04 (2H, d, J=8.6Hz),
7.3-8.0 (5H, m), 8.3-8.9 (3H, m), 9.9-10.1 (1H, m)
15 MASS (m/z): 1137 ($M^{+}+1$)
Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{84}\text{N}_{10}\text{O}_{15} \cdot 3\text{HCl} \cdot 8\text{H}_2\text{O}$:
C 48.36, H 7.46, N 10.07
Found: C 48.25, H 7.20, N 9.81

20 Example 206

- IR (KBr): 1699, 1678, 1651, 1539, 1514, 1456 cm^{-1}
MASS (m/z): 1264 ($M^{+}+1$)

25

30

35